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Tenth Annual Congress—April 5-9, 1954

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Contents for May-June, 1953

ANNALS of ALLERGY

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THE PROGRESS AND FUTURE OF THE AMERICAN COLLEGE OF ALLERGISTS

The Presidential Address

J. WARRICK THOMAS, M.D.
Richmond, Virginia

AS ONE of the Founders Group of The American College of Allergists, I share with you the realization that Allergy must be recognized as a specialty in its own right. It was because of this deep-seated conviction that the Founders built a liberal and democratic organization based on the need to fill an important gap in this aspect in the field of internal medicine. Recently I reviewed my correspondence with Dr. Fred W. Wittich pertinent to the organization of The College. In 1942 he stated that he wanted to organize a group of physicians who would make substantial contributions to allergy, leading it into its own field, as a specialty. Because it was necessary for someone to take the initiative, Dr. Wittich assumed this role, conferring with a number of allergists, the potential members of the Founders Group. He went on to say that he appreciated the confidence that these men had in his attempt to build an organization of this type.

It was the membership of The Forum on Allergy which was founded in Cincinnati in 1938, which initiated the idea of instructional courses known as the Forums on Allergy. I attended the first Forum which was conducted at Toledo, Ohio, in January, 1939, from whose membership the nucleus of the College of Allergists was chosen. Officers were elected, committees appointed, preparations were made for writing the Constitution and By-laws, and plans were drawn for incorporation. This was accomplished in November, 1942, when The College was incorporated as a non-profit organization in the State of Minnesota.

Presidential Address, Ninth Annual Congress, The American College of Allergists, April 28, 1953, Chicago, Illinois.

Dr. Thomas is Assistant Professor of Clinical Medicine, Medical College of Virginia, Richmond, Virginia.

I think it is worthwhile here to review the following aims and purposes of The College as set forth in the Charter:

A. The establishment of an organization of qualified medical men and scientists of good standing who shall meet from time to time for the purpose of promoting and advancing the study of research and clinical knowledge of allergy as it applies to the various specialties in medicine.
B. To maintain and advance the highest possible standards among those engaged in the practice of allergy.
C. To perpetuate the best conditions of medicine and medical ethics.
D. To establish standards for qualification and procedure for certification of men engaged in the specialty of allergy.
E. To maintain the dignity and efficiency of this specialty in its relation to public welfare.
F. To promote friendly intercourse among those engaged in the practice of allergy.

As a member of the first Board of Regents and of the committee which prepared the Constitution and By-laws, I keenly realized the need for building The College on a firm foundation. It was necessary that The College give proper recognition to Otolaryngologists, Ophthalmologists, Pediatricians, Dermatologists, Gastro-Enterologists, as well as Internists who were applying allergy in their practice of medicine. In addition to Fellowships, it was necessary to have Associate Fellowships for Immunologists, Bacteriologists, Pharmacologists, Biochemists, Botanists, and others, so that they, too, might receive just recognition. The initial membership at the time The College was organized was forty-five.

ANNALS OF ALLERGY

The first issue of ANNALS OF ALLERGY was published in July, 1943 as the official bi-monthly publication of The American College of Allergists. It was necessary that The College have a means of disseminating knowledge of allergy through the medium of a current journal containing departments representing all phases of the subject. The editorial in the first issue of the ANNALS outlined a threefold purpose, "First, to serve that large group of practitioners and specialists who had been applying allergy in their practice and to encourage a large group of the younger men who are already serious, earnest and enthusiastic workers in allergy."[1] The policy of the ANNALS was to be liberal and informal. It was to represent the serious workers in the field of allergy. Second, each issue of the ANNALS as it grew was to establish sections incorporating articles representing the results of current scientific research; practical articles on the diagnosis and treatment of allergic states; abstracts of important papers; editorials and current questions; ideas for procedures and apparatus, and Questions

and Answers. The Editorial Board was likewise to be divided into sections which would represent various phases of allergy. Third, to broaden the scope of allergy so that it might receive proper recognition as a distinct specialty."[1] The need for the ANNALS is appreciated when one notes that nearly all of the journals representing the different specialties of medicine publish papers on allergy as applied to their own specialty and showing a special interest in the subject.

The College Decennial Anniversary issue of the ANNALS carries an editorial[2] which summarizes the progress and accomplishments of The College over a ten-year period. The College has grown from a membership of forty-five at its inception to a present membership of more than 1,000 physicians, and among its members are outstanding allergists and leaders both in the investigative and the clinical fields of allergy and allied subjects. Many of these men hold key positions in important institutions of higher learning and are found as well on the staffs of accredited hospitals.

COLLEGE ACCOMPLISHMENTS

The College has pioneered in a number of outstanding accomplishments. It was the first allergy society to elect associates in Immunology, Biochemistry, Plant Pathology and Botany. The ANNALS was the first allergy journal to publish practical clinical papers, as well as articles on investigative allergy; and the first to have departments for editorials, questions and answers, news items, and comprehensive reviews of the literature. One of the unique services is the section, "Progress in Allergy." These articles entitled, "Progress in Allergy," are available as bound volumes. These include reviews of each of the manifestations of allergy as well as papers on Miscellaneous Allergy. The ANNALS OF ALLERGY has grown from the initial issue which averaged eighty-nine pages exclusive of eight pages of advertising to recent issues containing 140 pages with thirty-one pages of advertising. Today the mailing list totals 2,500.[2] Other College publications include four books, *Psychodynamics and the Allergic Patient, Allergy in Relation to Otolaryngology, Allergy in Relation to Pediatrics,* and *Allergic Pruritus, Its Dermatologic Management.* The *Quarterly Review of Allergy and Applied Immunology* is published under the auspices of The College and contains summaries of the important literature of the world. The bibliography on all subjects related to allergy, consists of thousands of references gathered by the eminent Dr. Jonathan Forman.

One of the most outstanding features of The College has been its keen appreciation of the need of postgraduate education and it was at the first annual meeting of The College in Chicago in 1944, that the first Postgraduate Instructional Course in Allergy was held. This has been continued annually for nine years. During this time the growth of the postgraduate courses offered by The College is demonstrated by the fact that at this meeting, there are more than seventy-five instructors for the in-

tensive three-day instructional course. The College has made available various fellowships at outstanding institutions. There have been additional steps in furthering research in the Field of Allergy.

One of the initial aims and purposes of The College was "To establish standards for the qualification as well as procedures for the certification of men engaged in the specialty of allergy," and we are happy today to note the coöperation of The College and The Academy in setting up a functioning joint Certification Committee on Allergy. This Committee has appeared annually for the past five years before the Committee on Standards of Medical Education and Licensure requesting an independent Board and rejecting Sub-Certification by The American Boards of Internal Medicine and Pediatrics. It is unfortunate for the specialty of allergy that a satisfactory solution regarding certification has to date not been achieved. It is felt by the majority of the members of both The College and The Academy that an Autonomous Board is warranted, and it is hoped that such a Board will be established in the very near future.

It is necessary that we maintain high educational standards in allergy so that we may continue to command the respect of all impartial physicians.

Education in allergy must proceed in three directions: undergraduate, postgraduate and lay education.[3] It is necessary for us to perpetuate this type of teaching through many channels, including medical societies and meetings, the specialized societies, state and national associations, regional medical groups including county and city medical societies or academies, and the medical schools, hospitals and clinics.

The College is proud to have equal representation with The Academy in the organization of The American Foundation for Allergic Diseases. This Foundation will make possible programs of public relations, through Speaker's Bureaus, programs of teaching, medical education and training of physicians to recognize and be able to cope with the problems of Allergy. It will help us to support Fellowships and residencies with trained, qualified clinicians in the Field of Allergy, and assist in establishing centers and facilities to carry out this work.[3]

The College is happy to have had so close a relationship with the International Association of Allergology which was organized in August 1945. Through the medium of the ANNALS OF ALLERGY announcements regarding the founding, as well as the development and subsequent report of the first meeting in Zurich, Switzerland, in September 1951 were outlined.

Over the past year, The College has enjoyed an amiable relationship with The Academy and through the joint efforts of both great progress is being realized as previously noted in the matter of certification, the establishment of The American Foundation for Allergic Diseases, and a cooperative scheduling of the annual meetings without conflicting dates. Furthermore the spirit of coöperation is exhibited in the joint effort which has resulted in a splendid program for the Allergy Section of the American Medical Association Meeting in New York in June 1953.

The future of allergy in medicine is unlimited. To realize this fully one has only to consider the publications in allergy which include some thirty-two authoritative books on the subject, the *Journal of Allergy*, the ANNALS OF ALLERGY, the *Quarterly Review of Allergy and Applied Immunology*, the *International Society of the Allergy Correspondence Club Letters*, the seven or more foreign medical journals, besides the many specialty journals which have sections on allergy or which publish numerous articles on the subject. The paramount accomplishment of The College to date is the fact that its founding and development has resulted in intensive educational programs and an ever increasing appreciation and recognition of allergy as a specialty resulting in better medical care through the consideration of an allergic factor in the management of some 16,000,000 people who today in the United States suffer from allergic disorders.[3]

Let us all strive to hold our standards high, to perpetuate a broad educational program, and dispense with personal ambitions, jealousies and animosities. Let us all be concerned primarily and as a first consideration with progress in allergy.

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2031 Monument Avenue

INSTRUCTIONAL COURSE TO BE HELD IN PARIS

An instructional course on allergic diseases will be held under the auspices of the Faculty of Medicine of the University of Paris at the Hospital Broussais, under the direction of Professor Pasteur Vallery-Radot. The course will extend from October 19 to 29, inclusive, 1953, and will consist of the theory and practice of allergy. The number of registrants is strictly limited. Those who wish to enroll are requested to write the Medical Clinic, Hospital Broussais, 96 rue Didot, Paris-XIVe. The price for the lecture course is 5,000 francs, and 8,000 francs for the lectures and practical demonstrations. Check should be enclosed with application.

On the morning of October 19, Dr. Bernard N. Halpern will conduct practical demonstrations of anaphylactic shock in various animal species, as well as the Arthus phenomenon. During the ten days there will be lectures and practical demonstrations of all phases of allergic diseases. The faculty consists of Professors Vallery-Radot, Gauthier-Villars, and Debré, and Doctors Halpern, Blamoutier, Holtzer, Wolfromm, Sidi, Grabar, and Lhermitte.

INCREASED FRAGILITY OF EOSINOPHILIC LEUKOCYTES UNDER THE INFLUENCE OF CORTISONE TREATMENT

DR. F. MARTINEZ CORTES, DR. M. SALAZAR MALLEN, F.A.C.A. (Hon.)
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THE SPECIFIC functions of the eosinophilic blood cells are still a matter of unsettled opinions. It has been claimed that these cells are the carriers of antigens,[3] or of histamine and other toxic materials,[1,8] and also that the formation of the eosinophilic granulations is the result of the combination of antigen and its antibody.[4] The facts are that an increased number of eosinophilic blood cells is present in many cases of allergic sensitization and that the use of ACTH or cortisone results in a prompt drop or disappearance of the circulating eosinophilic leucocytes.

The eosinopenia can be attributed to:

1. A decrease of the rate of eosinophil formation because of the action of the hormones;

2. An increase in the rate of eosinophil destruction by peripheral organs such as the spleen, and

3. An increased fragility of the eosinophils themselves leading to their quicker disappearance from the blood stream.

The first possibility has not received experimental support, since it has not been possible to demonstrate decreased eosinophil formation, under the influence of ACTH or cortisone.[6] The second and third alternatives can complement each other, since the diminishing of the circulating eosinophils, if not due to the cells' localization in periphereal organs, such as the spleen,[2,7] could be explained as a result of the existence of degenerative changes in the cells themselves, facilitating their increased disposal and elimination. In a recent communication Padawer and Gordon,[5] show that rats having received ACTH or cortisone yield exudates whose eosinophils show definite degenerative changes leading to their disintegration and macrophage phagocytosis.

Independent of the latter work and impressed by the strikingly different behaviour of the eosinophilic cells from different blood samples when observed at different times in the counting chamber, we decided to carry on experiments to look for a possible increased *in vitro* fragility of the same cells from individuals under the influence of cortisone. Whereas this type of study is far from reproducing the *in vivo* conditions leading to eosinopenia, it nevertheless may show some measure of the cells' fragility under complex circumstances such as room temperature and the presence

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TABLE I. EOSINOPHIL DISAPPEARANCE (*in vitro*) BEFORE AND AFTER THE USE OF CORTISONE

Cases	Experiment	Before Cortisone			After Cortisone			X^2	p(N:1)
		Initial	Final	Dif. %	Initial	Final	Dif. %		
I.	1	270	187	30.74	72	31	56.90	3.70 bet.	5-10%
	2	65	48	26.10	55	20	63.63	4.18 bet.	2- 5%
II.	1	71	46	35.21	14	4	71.42	1.29 bet.	20-30%
	2	79	49	37.97	19	7	63.15	0.76 bet.	30-50%
III.	1	109	82	24.77	57	27	52.63	0.02 bet.	70-90%
	2	86	61	29.06	40	18	55.00	1.05 bet.	30-50%
IV.	1	152	130	16.92	131	88	32.82	2.41 bet.	10-20%
	2	147	124	15.64	110	68	38.18	2.20 bet.	10-20%
V.	1	56	40	28.77	20	8	60.00	1.06 bet.	30-50%
	2	50	41	22.50	14	6	57.14	0.76 bet.	30-50%
VI.	1	33	13	60.60	2	0	—	—	—
	2	30	14	53.33	1	0	—	—	—

Averages 31.78± 13.26 55.08 (10 cases) ±11.59.
S. D. of dif. 17.6 (not significant).

of eosine and other chemical (nonphysiological) substances in the diluting fluid.

CASE MATERIAL AND TECHNIQUE EMPLOYED

Six normal healthy individuals were studied. In each case four blood samples were obtained by venipuncture, care being taken to make the bleedings under conditions as uniform as possible in regard to rest and hour for the performance of the test. Five cubic centimeters of venous blood were collected on heparin and centrifuged at 2,500 r.p.m., for ten minutes. The leukocytes layer, through convenient dilution with Randolph's fluid, was used to make the counts. Three minutes after the filling up of the Neubauer chamber, the first or initial count of all cells within the entire ruled area was performed; successive counts were later made every thirty minutes up to four hours (final count.)

Two of the samples were obtained without cortisone administration, on successive days; the other two corresponded to bleedings from four hours after ingestion of 50 mg of cortisone acetate.

RESULTS

Table I, above shows the results of the experiment, giving only data in relation to the initial and final counts:

CONCLUSION

In all cases cortisone administration resulted in the well-known eosinopenic response. An average decrease of 31.78 per cent ± 13.26 cells was observed in samples from individuals without cortisone influence, while in the group of those having received it, the decrease was 55.08 per cent ± 11.59. The difference between both figures is not significant at the 5 per cent level, but in view of the constant tendency towards greater decrease of eosinophil numbers after cortisone, under the conditions outlined,

it is suggested that the drug effectively reduces eosinophilia through the production of an increase of the cells' fragility leading to their macrophage disposal.

SUMMARY

Disappearance *in vitro* of blood eosinophil cells was studied in six normal individuals, before and after cortisone administration. In all twelve experiments, a greater destruction of the cells after the drug was taken was noted; the differences between the two sets of experiments not being, however, statistically significant at the 5 per cent level. The data presented are therefore considered as only suggestive of cortisone action upon the eosinophil fragility.

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Montes Urales 765 (Dr. Mallen)

RESPIRATORY AND PHYSICAL EXERCISE IN THE TREATMENT OF BRONCHIAL ASTHMA

BERNARD T. FEIN, M.D., F.A.C.A., and EUGENIA P. COX, B.A.
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and
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THE IMPORTANCE of physical methods of improving respiration has become more evident since the prevalence of poliomyelitis epidemics throughout the country. These physical methods have been utilized to eliminate obstructions and mucous plugs in order to prevent atelectasis and pneumonia. The success of these physical and mechanical methods of assisting respiration has stimulated investigation[4,5] as to their importance in bronchial asthma.

It is well known that in normal breathing the respiratory muscles alter the configuration of the thorax so that on inspiration, air inflates the lungs. This air is expelled by the elastic recoil of the lungs with each expiration. In the asthmatic paroxysm, inspiration becomes easier than expiration due to the generalized spasm of the smooth muscle in the bronchioles and subsequent edema of the mucosa. The lungs become more and more distended to their maximum capacity. This condition is termed emphysema. The thoracic cage is held in a state of overdistention which returns to normal after the attack. If, however, the attacks are of long duration and occur frequently, the chest adapts itself to the condition of the lungs and assumes a barrel shape with widening of the costal angles. The muscles of the chest become so accustomed to this position that the chest wall does not return to normal following an attack.

Some workers[9,15] as long ago as 1935 recommended physical methods of attempting to correct this condition. Some men[1,3,8,10] have incorporated these and other procedures to alter and prevent the production of emphysema. The vast experience[13] of the thoracic surgical services in World War II has illustrated the value of respiratory and physical exercise in the complete rehabilitation of the injured chest. Many mechanical methods of improving respiration have been introduced. Some are economically unavailable to most patients. These mechanical methods include the intermittent positive pressure-breathing apparatus,[7] the repetimeter,[14] and the exsufflator.[6]

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Dr. Fein is chief of Allergy Clinic, Veterans Administration Regional Office, San Antonio, Texas.
Miss Cox is chief of Physical Therapy Department, Veterans Administration Regional Office, San Antonio, Texas.
Miss Green is chief of Physical Therapy Department, Veterans Administration Hospital, Iowa City, Iowa.
Presented before the Ninth Annual Congress of the American College of Allergists, Chicago, Illinois, April 27, 1953.

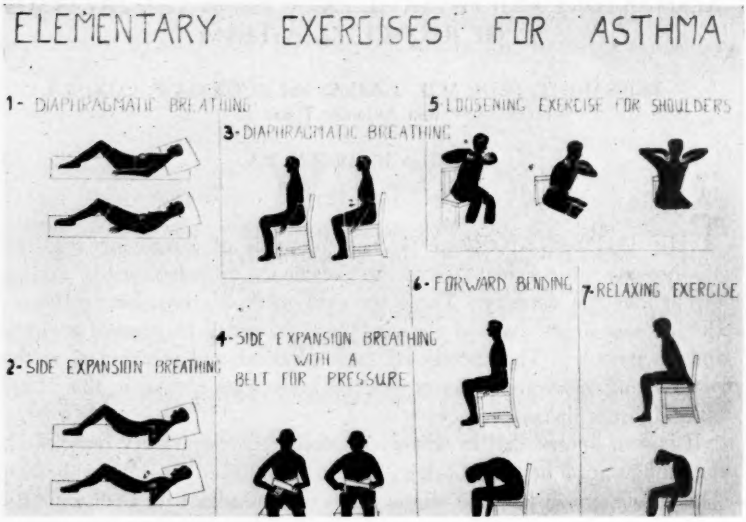

Fig. 1.

In the early cases of asthma, the chest muscles have not been altered by overdistended lungs and the early introduction of exercise is advocated as a preventive measure. In the chronic cases, breathing is done almost entirely with the upper part of the chest, the lower being immobile and the diaphragm used very slightly. Exercises are used to teach the patient to avail himself of the lower part of his chest as well as the upper, and also his diaphragm to a much greater extent than is normal.

These exercises are advocated as a supplementary measure and not as a substitute for allergic or medical therapy or to replace well-established procedures. This paper thus is presented as an attempt to evaluate the respiratory and physical exercises.

MATERIAL

An examination was made on thirty patients selected from the Allergy Clinic. All the patients were male veterans ranging in age from twenty-five to sixty-three years. The patients all had a record of having been discharged from the service for bronchial asthma, either during World War I, World War II, or the Korean War. They were seen at the Allergy Clinic on an average of once or twice a week. They had all been given a complete interview, physical examination, and laboratory tests which included a nasal smear for eosinophils, a vital capacity test, x-ray of the accessory nasal sinuses, and a chest x-ray. All the patients had been under allergy management from eighteen to twenty-four months prior to the introduction of physical exercises.

Three groups of patients were studied:

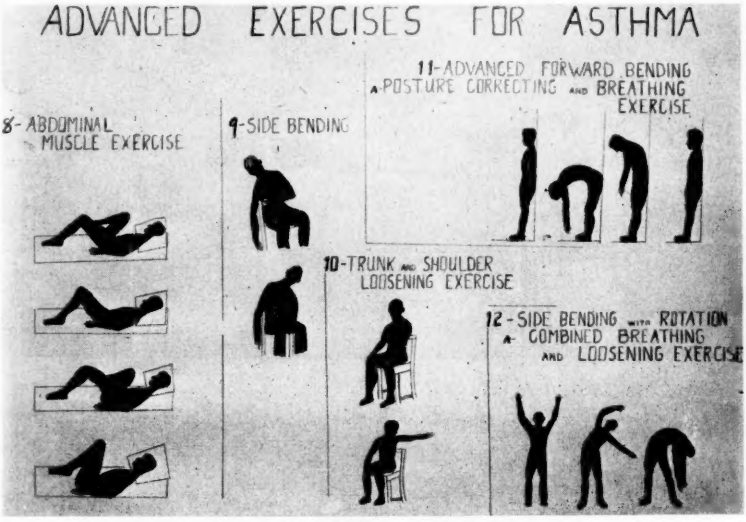

Fig. 2.

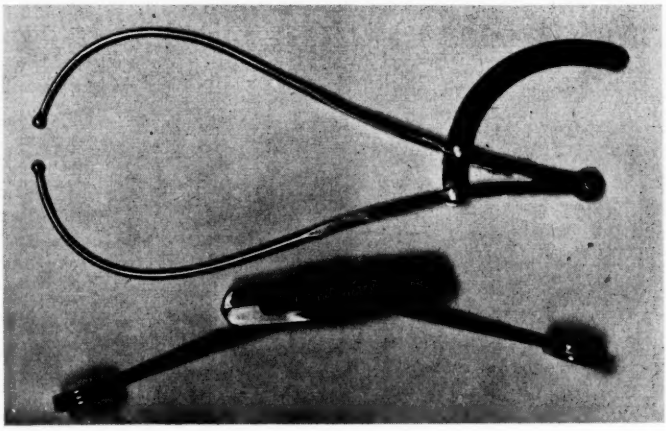

Fig. 3.

Group I, Special Exercise Group, consisted of five patients who were followed in the allergy and physio-therapy departments at bi-weekly intervals for one year.

Group II, Home Exercise Group, consisted of ten patients who received four supervised exercise periods in the physiotherapy department and conducted all subsequent exercise periods once or twice daily at home.

Group III, Control Group, consisted of fifteen patients followed in the Allergy Clinic once or twice a week and received desensitization treatments only.

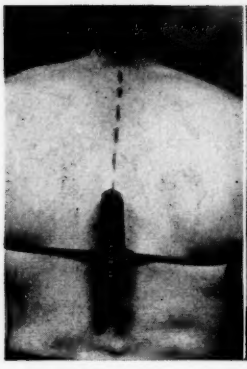

Fig. 4.

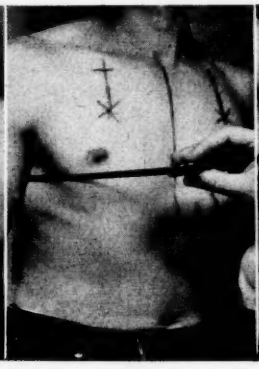

Fig. 5.

Fig. 6.

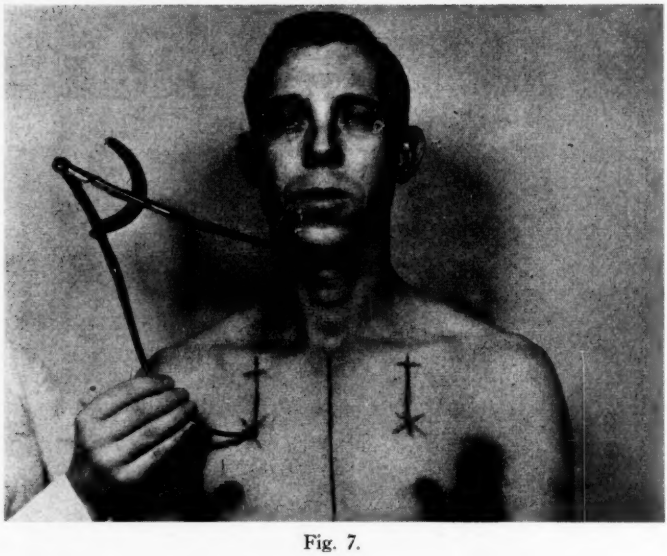

Fig. 7.

METHOD

The routine of respiratory and physical exercises used have been outlined completely by the Asthma Research Council of London, England,[2] and are seen in Figures 1 and 2. The exercises are divided into two large groups, the elementary and advanced. Other routines have been advocated[16] for children which are similar in many respects to the adult exercises. The patients were taught the exercises during ten-minute supervised periods and were advised to practice at home until the next period. They were told to perform the exercises in the morning before breakfast, at night before bedtime, and at the first evidence of an impending attack of

asthma. They were given twelve exercise groups which were learned under the supervision of a physio-therapist. On the third visit, hemithorax measurements were taken and performed every two months during the course of one year.

The hemithorax measurements were obtained by using the expansometer and the chest caliper as shown in Figure 3. The chest expansometer was introduced[11] as a measuring device to measure both halves of the chest simultaneously in order to determine the excursion of each side, and thereby reveal the lack of normal movement of each half. The chest caliper is a standard pelvimeter modified[12] to accurately measure the movements of the upper segments of the chest. The lower segments of the thorax with posterior displacement of the expansometer is seen in Figures 4, 5, and 6, the spinous processes of the seventh cervical vertebrae and the first ten thoracic vertebra having been marked. The lower chest measurements are taken simultaneously at the level of the tenth thoracic spine. The upper segments of the thorax measured with the chest caliper placed on the skin mark two inches below the mid-clavicular line anteriorly, and the spinous process of the second thoracic vertebra posteriorly, as seen in Figure 7.

RESULTS

Table I shows the hemithorax measurements during the last three months in *Case No. 1.* There has been an increased ability to expand the upper and lower segments of the chest and the patient has been able to learn to immobilize his chest completely during controlled breathing. During controlled breathing, he is able to limit expansion of the upper segments of the chest. Table II shows the recorded results during the last six months in *Case No. 2.* These results are similar to *Case No. 1.* Table III is a summary of *Case No. 3,* and although there has been an increased ability to expand the chest, the patient has been unable to learn complete immobilization of the chest during controlled breathing. Table IV, *Case No. 4,* shows an increased ability to greater expansion in the upper segments of the chest but not in the lower part. Despite this, the patient was able to learn excellent diaphragm control and to immobilize the chest during this controlled breathing. Table V shows the hemithorax measurements of *Case No. 5,* the most severe case of the entire series. He was able to increase over-all chest expansion, only slightly, and was unable to master controlled (diaphragmatic) breathing.

Table VI is a summary of the Special Exercise Group, given an average of twenty-six supervised instruction periods during the course of one year. Five cases (100 per cent) were able to increase chest expansion in the upper chest; three cases (60 per cent) were able to increase expansion in the upper and lower chest, and three cases (60 per cent) were able to learn controlled (diaphragmatic breathing). Three cases (60 per cent) were able to abort mild paroxysms of asthma.

TABLE I. HEMITHORAX MEASUREMENTS

Case No. 1			Regular Breathing				Diaphragmatic Breathing			
Date	Level	Position of Chest	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches
9-10-52	Seventh Thoracic Vertebra	Inspiration	18 1/2	19	37 1/2	3/4	17 3/4	18 1/2	36 1/4	1/2
		Expiration	18	18 3/4	36 3/4		17 1/2	18 1/4	35 3/4	
11- 6-52		Inspiration	18 3/4	19	37 3/4	1 1/2	17 3/4	18 1/2	36 1/4	1/2
		Expiration	18	18 1/4	36 1/4		17 1/2	18 1/4	35 3/4	
12-18-52		Inspiration	18 1/2	18 3/4	37 1/4	1 3/8	18 1/4	18 1/2	36 3/4	0
		Expiration	17 5/8	18	35 5/8		18 1/4	18 1/4	36 3/4	
9-10-52	Tenth Thoracic Vertebra	Inspiration	17 1/2	18 1/4	35 3/4	3/4	17 5/8	18 1/2	36 1/8	5/8
		Expiration	17	18	35		17 1/4	18 1/4	35 1/2	
11- 6-52		Inspiration	18	18 3/4	36 3/4	1	17 5/8	18 3/8	36	1/2
		Expiration	17 1/4	18 1/4	35 3/4		17 3/8	18 1/8	35 1/2	
12-18-52		Inspiration	17	19	36	1 1/2	16 5/8	18 3/8	35	0
		Expiration	16 1/2	18 1/4	34 3/4		16 5/8	18 3/8	35	
9-10-52	Second Thoracic Vertebra	Inspiration	7 1/8	7 1/8			6 3/4	6 3/4		
		Expiration	7	7			6 5/8	6 5/8		
11- 6-52		Inspiration	7 1/8	7 1/8			6 1/2	6 1/2		
		Expiration	7	7			6 3/8	6 3/8		
12-18-52		Inspiration	7 1/2	7 1/2			6 1/2	6 1/2		
		Expiration	7 1/4	7 1/4			6 1/2	6 1/2		

TABLE II. HEMITHORAX MEASUREMENTS

Case No. 2			Regular Breathing				Diaphragmatic Breathing			
Date	Level	Position of Chest	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches
6-12-52	Seventh Thoracic Vertebra	Inspiration	21	22	43	¾	21 ½	20 ½	42	½
		Expiration	20 ¾	21 ½	42 ¼		21 ¼	20 ¼	41 ½	
8-14-52		Inspiration					21 ¾	20 ¼	42	½
		Expiration					21 ½	20	41 ½	
10- 9-52		Inspiration	22 ¼	21 ¼	43 ½	1 ½	21 ⅜	21 ⅝	42	½
		Expiration	21 ¼	20 ¾	42		21 ⅛	20 ⅜	41 ½	
12-18-52		Inspiration	22	20 ½	42 ½	1	22	21	43	0
		Expiration	21 ½	20	41 ½		22	21	43	
6-12-52	Tenth Thoracic Vertebra	Inspiration	20 ¾	20 ¼	41	½	21 ¼	20	41 ¾	½
		Expiration	20 ⅜	20 ⅛	40 ½		21	19 ¾	40 ¾	
8-14-52		Inspiration					21 ⅜	20 ¼	41 ½	⅜
		Expiration					21 ⅛	20	41 ⅛	
10- 9-52		Inspiration	20 ½	21	41 ½	1 ¼	21 ¼	20 ⅝	41 ¾	¼
		Expiration	20	20 ¼	40 ¼		21	20 ½	41 ½	
12-18-52		Inspiration	22 ¼	20 ¼	42 ¾	1 ¾	21 ⅞	20 ¼	42 ⅛	0
		Expiration	21 ½	19 ¾	41		21 ⅞	20 ¼	42 ⅛	
6-12-52	Second Thoracic Vertebra	Inspiration	8	8			7 ⅜	7 ⅜		
		Expiration	7 ¾	7 ¾			7 ¼	7 ¼		
8-14-52		Inspiration					7 ½	7 ½		
		Expiration					7 ¼	7 ¼		
10- 9-52		Inspiration	8 ⅛	8			7 ⅝	7 ¾		
		Expiration	7 ⅝	7 ½			7 ¼	7 ¼		
12-18-52		Inspiration	8 ½	7 ¾			8 ¼	7 ½		
		Expiration	8	7 ½			8 ¼	7 ¼		

TABLE III. HEMITHORAX MEASUREMENTS

Case No. 3			Regular Breathing				Diaphragmatic Breathing			
Date	Level	Position of Chest	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. In Inches	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches
6-12-52	Seventh Thoracic Vertebra	Inspiration	19	17 1/2	36 1/2	3/4	18 1/4	17 3/8	35 5/8	3/8
		Expiration	18 5/8	17 1/8	35 3/4		18	17 1/4	35 1/4	
8-15-52		Inspiration					17 1/4	17 3/8	35 5/8	3/8
		Expiration					17	17 1/4	34 1/4	
10- 9-52		Inspiration	19 1/2	17 5/8	37 1/8	1 5/8	17 3/8	17 3/8	35 5/8	5/8
		Expiration	18 1/2	17	35 1/2		18	17	35	
12- 8-52		Inspiration	19	17 3/4	36 3/4	2 1/4	18 3/4	17 3/4	36 1/2	2
		Expiration	17 3/4	16 3/4	34 1/2		17 3/4	16 3/4	34 1/2	
6-12-52	Tenth Thoracic Vertebra	Inspiration	17 1/2	16 1/2	34	1/4	16 3/4	17 3/8	34 1/8	1/4
		Expiration	17 3/8	16 3/8	33 3/4		16 5/8	17 1/4	33 7/8	
8-15-52		Inspiration					17 1/2	16 3/8	33 7/8	3/8
		Expiration					17 1/4	16 1/4	33 1/2	
10- 9-52		Inspiration	17 1/2	16 5/8	34 1/8	1	16 3/4	16 5/8	33 3/8	1 1/8
		Expiration	17	16 1/8	33 1/8		16 1/8	16 1/8	32 1/4	
12- 8-52		Inspiration	17 1/4	17 1/4	34 1/2	2	18	17 1/4	35 1/4	1 3/4
		Expiration	16 1/4	16 1/4	32 1/2		17 1/4	16 1/4	33 1/2	
6-12-52	Second Thoracic Vertebra	Inspiration	7	7			7	7		
		Expiration	6 3/4	6 3/4			7	7		
8-15-52		Inspiration					7	7		
		Expiration					7	7		
10- 9-52		Inspiration	7 1/4	7 1/8			6 5/8	6 3/4		
		Expiration	7 1/8	6 3/4			6 1/2	6 5/8		
12- 8-52		Inspiration	7 1/4	7			7 1/4	6 1/2		
		Expiration	6 1/4	6 3/4			6 1/2	6		

TABLE IV. HEMITHORAX MEASUREMENTS

Case No. 4			Regular Breathing				Diaphragmatic Breathing			
Date	Level	Position of Chest	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches
6-26-52	Seventh Thoracic Vertebra	Inspiration	18 1/2	19 1/4	38 3/4	3/4	18 3/4	18 3/4	37 1/2	1/2
		Expiration	19	19	38		18 1/2	18 1/2	37	
8-21-52		Inspiration					19 1/2	20	39 1/2	1/2
		Expiration					19 1/2	19 3/4	39	
10- 9-52		Inspiration	20 3/4	19 3/4	40 1/2	1 1/4	20 1/8	19 3/8	39 1/2	5/8
		Expiration	20	19 1/4	39 1/4		19 3/4	18 1/8	38 7/8	
12-11-52		Inspiration	19 1/2	19	38 1/4	1 3/4	19	19	38	0
		Expiration	18 3/4	17 3/4	36 1/2		19	19	38	
6-26-52	Tenth Thoracic Vertebra	Inspiration	19 7/8	19	38 7/8	3/8	19 1/2	19 7/8	39 3/8	3/8
		Expiration	19 3/4	18 3/4	38 1/2		19 3/8	19 5/8	39	
8-21-52		Inspiration					19	19 1/2	38 1/2	1/2
		Expiration					18 3/4	19 1/4	38	
10- 9-52		Inspiration	19 7/8	19	38 7/8	3/8	19 5/8	18 5/8	38 1/4	1/2
		Expiration	19 3/4	18 3/4	38 1/2		18 3/8	18 3/8	37 3/4	
12-11-52		Inspiration	19 5/8	19	38 5/8	3/8	19	19	38	0
		Expiration	19 1/4	18 1/2	38 1/4		19	19	38	
6-26-52	Second Thoracic Vertebra	Inspiration	7	7			6 1/2	6 1/2		
		Expiration	6 3/4	6 3/4			6 3/8	6 3/8		
8-21-52		Inspiration					6 7/8	6 7/8		
		Expiration					6 3/4	6 3/4		
10- 9-52		Inspiration	7	7			6 7/8	6 7/8		
		Expiration	6 1/2	6 1/2			6 3/4	6 3/4		
12-11-52		Inspiration	7 1/2	7			7 1/8	7		
		Expiration	7 1/4	6 3/4			7	6 7/8		

TABLE V. HEMITHORAX MEASUREMENTS

Case No. 5			Regular Breathing				Diaphragmatic Breathing			
Date	Level	Position of Chest	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches	Right Chest in Inches	Left Chest in Inches	Total Expan. in Inches	Diff. in Inches
7-22-52	Seventh Thoracic Vertebra	Inspiration	22 1/2	22	44 1/2	1	22 1/2	21 3/4	44 1/4	3/4
		Expiration	22	21 1/2	43 1/2		22	21 1/2	43 1/2	
10- 6-52		Inspiration	22 3/4	22 1/2	45 1/2	1	22 3/4	22 1/2	45 1/4	1/2
		Expiration	22 1/2	22	44 1/4		22 1/2	22 1/4	44 3/4	
12- 8-52		Inspiration	22	22	44 3/4	1 1/2	22 1/4	22 1/2	44 3/4	1
		Expiration	20 1/2	21 3/4	43 1/4		22	22	43 3/4	
7-24-52	Tenth Thoracic Vertebra	Inspiration	21 1/4	20 3/4	42	1	21 1/4	20 3/4	42	1/2
		Expiration	20 3/4	20 1/4	41		21	20 1/2	41 1/2	
10- 6-52		Inspiration	21 1/4	20 7/8	42 1/8	3/8	21 3/8	21 1/4	42 5/8	3/8
		Expiration	21	20 3/4	41 3/4		21 1/4	21	42 1/2	
12- 8-52		Inspiration	21 1/4	21 3/4	43	3/8	21 1/4	21	42 1/2	3/8
		Expiration	21	21 5/8	42 5/8		21 1/8	20 3/4	41 7/8	
7-24-52	Second Thoracic Vertebra	Inspiration	8 1/4	7 3/4			7 3/4	7 1/2		
		Expiration	7 3/4	7 1/4			7 1/2	7 1/4		
10- 6-52		Inspiration	8	8			7 1/2	7 3/4		
		Expiration	7 1/2	7 1/2			7 1/4	7 1/2		
12- 8-52		Inspiration	7 3/4	7 1/4			8	7 3/4		
		Expiration	7 1/2	7			7 3/4	7 1/2		

TABLE VI. SPECIAL EXERCISE GROUP

Case No.	Age	Number of Supervised Periods	Number of Supervised Hours	Decreased Chest Movements at Seventh Level	Increased Chest Movements at Tenth Level	Complete Immobilization of Chest During Exercises	Increased Chest Expansion at Seventh and Tenth Level	Exercises Employed to Abort Paroxysms	Vital Capacity Per Cent	
									Dec. 1951	Dec. 1952
1	58	19	5	Yes	Yes	Yes in 4 Mo.	Yes	None	89	89
2	32	17	4.5	Yes	Yes	Yes in 6 Mo.	Yes	Exercise No. 8	98	98
3	46	22	4.75	No	Yes	No	Yes	Exercise No. 8	52	71
4	61	40	10.25	Yes	Yes	Yes in 12 Mo.	Yes	Exercise No. 3	48	57
5	46	31	8	No	Yes	No	Yes	None	65	51

TABLE VII. HOME EXERCISE GROUP

Case No.	Age	Number of Supervised Periods	Number of Daily Exercise Periods at Home	Decreased Chest Movements at Seventh Level	Increased Chest Movements at Tenth Level	Complete Immobilization of Chest During Exercises	Increased Chest Expansion at Seventh and Tenth Level	Vital Capacity Per Cent	
								Dec. 1951	Dec. 1952
6	60	3	1	No	No	No	No	50	46
7	61	8	2	Yes	Yes	No	Yes	62	64
8	57	8	1	No	No	No	No	74	72
9	60	13	1	No	No	No	No	84	88
10	58	4	1	No	No	No	No	50	57
11	43	4	2	Yes	Yes	No	Yes	90	90
12	28	4	2	Yes	Yes	No	Yes	108	108
13	29	4	2	Yes	Yes	No	Yes	100	100
14	38	4	2	Yes	Yes	No	Yes	74	70
15	28	4	2	Yes	Yes	No	Yes	98	98

TABLE VIII. CONTROL GROUP

Case No.	Age	Number of Supervised Periods	Change in Hemithorax Measurements	Vital Capacity Per Cent	
				Dec. 1951	Dec. 1952
16	29	None	None	72	72
17	41	None	None	63	68
18	35	None	None	86	86
19	38	None	None	75	80
20	33	None	None	91	90
21	36	None	None	84	86
22	36	None	None	77	80
23	33	None	None	90	93
24	25	None	None	90	90
25	33	None	None	99	100
26	63	None	None	56	50
27	56	None	None	62	66
28	55	None	None	74	74
29	54	None	None	48	44
30	56	None	None	60	48

Table VII is a summary of the findings in the Home Exercise Group. It is seen that six cases (60 per cent) were able to increase chest expansion. No cases (0 per cent) were able to master controlled (diaphragmatic) respiration.

Table VIII is a summary of the Control Group who received no exercise. This group showed no permanent change in hemithorax measurements or the ability to improve the chest expansion.

DISCUSSION

Any treatment which is easily available and will benefit the complicated asthmatic condition must be employed to prevent further complications. Respiratory and physical exercises have been advocated by many as this type of treatment. It is seen that patients under regular supervision, together with home exercise, obtain the best results. The hemithorax measurement is not an ideal method of evaluation of the improvement in breathing capacity, but serves as the best index to the physical therapist. These measurements, together with the maximum breathing capacity, may serve as the best measurement of the degree of bronchial obstruction in asthma. The treatments require special supervision which is most readily available in institutions where physical therapy departments are well established. The time required to master breathing exercises varies with the individual and it is seen that a great deal more time is required in training for those persons whose vital capacity is below 80 per cent.

SUMMARY

1. Respiratory and physical exercises although beneficial, require long and close supervision to be of any value in preventing complications in asthma.

2. Hemithorax measurements are not ideal indices for evaluation of improvement in breathing capacity, but serve the physical therapist, better than when pulmonary function tests are done.

3. The time required to master controlled breathing varies greatly with the individual but once mastered, gives the patient a sense of security which enables him to abort mild attacks of asthma.

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1422 Nix Professional Bldg. (Dr. Fein)

NEW COLLEGE ROSTER

Questionnaires have been sent out to all members of the College for information to be published in the first College roster. This roster will be complete, and will contain much valuable information about the College since its inception.

A large number have already returned their questionnaires. If you have any added information pertinent to this questionnaire, please send it at once to headquarters, 401 LaSalle Medical Building, Minneapolis 2, Minnesota. Those who have not yet returned their questionnaires are requested to do so immediately.

AN ESTIMATION OF THE VALUE OF 3, 4 DIHYDROXYCHALCONE IN CLINICAL ALLERGY

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ONE THEORY of the pathogenesis of allergic reactions depends upon the acceptance of tissue formation of histamine as an important link in the response to allergens. In 1936, Werle[8] demonstrated the formation of histamine from the amino acid histidine by rabbit kidney slices. Demonstration of the existence of histidine decarboxylase in animal tissues[3,9] confirmed his work. On this basis administration of a drug which would successfully block histidine decarboxylase should be useful in the treatment of patients with allergic diseases.

Martin, Graf, Brendel, and Beiler[5] found vitamin P compounds inhibiting to histidine decarboxylase *in vitro*. They demonstrated d-catechin to be the most effective compound tested. This action was later demonstrated for the flavonoid 2', 3-4 trihydroxychalcone.[1] It was suggested that this action occurred through the formation of quinones.

In vivo experiments in guinea pigs with d-catechin demonstrated protection against the anaphylaxis produced in sensitized animals[6] by horse serum. In human beings, flavonoids have been combined with Dimapp (Phenergan) in several studies.[2,4,7] In general, these studies suggest that the flavonoid derivative has no effect itself, but through a synergistic action, may decrease the number of side reactions to the antihistaminic.

METHODS

1. Passive transfer reaction: Eight sensitized sites (0.1 cc each) were prepared in two recipients known to have skins capable of showing sensitivity. Using adjacent nonsensitized skin areas for injections of the control, the sites were tested with ragweed pollen extract as presented in Table I. Each subject ingested two 0.5 gm tablets of 3, 4 dihydroxychalcone four times daily for one week and four tablets one hour before the final test.

2. Clinical evaluation with 3, 4 dihydroxychalcone alone: Twenty-three allergy patients were given the drug, usually for periods of one week. Twelve patients had seasonal hay fever, nine had nonseasonal rhinitis, and two had atopic dermatitis. The doses were 1.5 gm daily in eight patients, 1 gm daily in twelve patients and 0.5 to 1 gm daily in three patients. The evaluation of the effectiveness of the treatment was determined by the patient's opinion of his or her well-being.

3. Clinical evaluation of 3, 4 dihydroxychalcone with and without Pyribenzamine: Twenty patients with seasonal hay fever (Ragweed Pollinosis) were used in this evaluation. These patients received pre-seasonal

From the Allergy Clinics, Jefferson Hospital and Temple Hospital, Philadelphia, Pennsylvania.

TABLE I.

	Subject 1		Subject 2		
	Before	After	Before	After	Control
R .0001	Neg.	Neg.	Slt.	Slt.	Neg.
R .001	Slt.	Slt.	Slt.	Slt.	Neg.
R .01	Mod.	Mod.	Mod.	Mod.	Neg.
R .1	Mkd.	Mkd.	Mkd.	Mkd.	Neg.

or co-seasonal injections of pollen extract and were studied during the ragweed pollen season. The patients received two tablets (0.5 gm of 3, 4 dihydroxychalcone or a placebo) four times daily for one week. Equal numbers of patients received the 3, 4 dihydroxychalcone and placebo each week. Approximately one half of each group also received Pyribenzamine tablets 50 mg every four hours while awake. Only those patients receiving both the placebo and 3, 4 dihydroxychalcone were included in the evaluation. The double blind fold technique was used. Daily reports were made on a card by the patient as to whether he had a bad twenty-four hours or a good twenty-four hours. The evaluation was made on the basis of the good and bad days recorded by the patients.

RESULTS

1. The results upon the passive transfer reaction are shown in Table I. There is no difference between the original reactions and those after treatment, indicating that the drug apparently had no effect in preventing the allergic reaction, even in a minor degree.

2. Only two of the patients receiving 3, 4 dihydroxychalcone alone reported beneficial results possibly related to the exhibition of the agent. All patients considered antihistamine therapy more effective.

3. Administration of either the placebo or the 3, 4 dihyroxychalcone was associated with 76 per cent good days and 24 per cent bad days. No evidence of potentiation of the effects of Pyribenzamine was observed. A decrease in the side actions of the antihistaminic was not reported by any patient. Two patients not included developed abdominal discomfort during 3, 4 dihydroxychalcone therapy and stopped their treatment.

DISCUSSION

These results are in keeping with the previously reported clinical results in so far as response to the flavonoid alone is concerned, however, no evidence of potentiation of Pyribenzamine effects or decrease in side actions from this antihistaminic were noted. It may be that the responses to Phenergan are altered.

SUMMARY

Several vitamin P compounds have been shown to inhibit histidine decarboxylase *in vitro*. Flavonoids have also been used in human beings with the thought of alleviating allergic symptoms. The present study is intended

to determine the efficacy of one of the flavonoids, 3, 4 dihydroxychalcone, in allergy. The usual dose taken was 0.5 gm four times daily. Such doses had no effect on the passive transfer reaction of sites sensitized to ragweed pollen on the administration of pollen extract in different dilutions. Of twenty-three allergy patients with seasonal hay fever, nonseasonal rhinitis, or atopic dermatitis only two reported any possible benefit. Twenty patients with ragweed pollinosis received the chalcone for one week and a placebo for another during the pollen season. The double blindfold technique was used. The evaluation was made on the basis of good and bad days reported on a card, by the patients. The possibility of synergism between the chalcone and Pyribenzamine was also studied.

CONCLUSIONS

1. 3, 4 dihydroxychalcone does not appear to be effective in clinical allergy.
2. 3, 4 dihydroxychalcone neither potentiated the effects, nor decreased the frequency of side reactions to Pyribenzamine.

ACKNOWLEDGMENT

We wish to thank Steven Horoschak, National Drug Company, for a generous supply of 3, 4 dihydroxychalcone; and Dr. Harry L. Rogers for his assistance in part of this work.

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A COMMONSENSE APPROACH TO PSYCHOTHERAPY IN ALLERGIC PRACTICE

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OVER A period of years, some allergists with whom I have spoken have become increasingly disturbed about the role they should play in the treatment of patients who consult them. The substance of their quandary may be summarized as follows: "We want to be allergists, but with all this talk about psychosomatic factors in allergy, do we have to become psychiatrists also?" In an attempt to answer this question, I have set down a few basic ideas which may clarify some of the issues involved.

An allergist is a physician skilled in the art and science of diagnosis and treatment of particularly troublesome and sometimes elusive clinical entities which today we call allergies.[19,20] A patient consults an allergist because a referring physician—or the patient himself—believes that his disorder has an allergic basis, and because the allergist is the specialist who is expert in this field. Furthermore, the patient expects that after his examination is completed, the allergist will make a diagnosis. If he is found to be allergic, the patient will expect treatment which will relieve his symptoms or even effect a cure. When the allergist accomplishes this, he has done his job well. And that's all there is to it—or would be, if patients were not also reactive human beings.[11,12,13]

Every patient is reacting emotionally all the time: to his own thoughts, ideas and personal problems; to his past and present life experiences; to his anticipation of future problems; to his allergic illness; to his medical treatment; and even to his allergist. Sometimes these emotional reactions produce unpleasant symptoms and signs which are difficult to distinguish from allergic illnesses. In certain patients, specific untoward emotional disturbances may cause changes in those tissues which constitute the final common pathway of both allergic and emotional reactions in a direction which can transform a minor allergic reaction or even a subclinical allergy into a fulminant condition which may require emergency therapy.[2,8,9,13,21]

A patient who develops his first severe, unanticipated allergic illness may begin experiencing all sorts of emotional reactions, not only to his allergic illness, but also to worry about possible future recurrences of his allergic trouble. These anxieties and fears in turn may create other serious psychological and behavior problems which may outlast his already-experienced allergic illness.[17]

The intensity and extensiveness of a patient's emotional reaction to his allergies depends on his basic personality structure, on the site of allergic involvement, on the severity, duration and frequency of his allergic reac-

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tions, and on whether or not he knows the nature of the allergenic agent which precipitated his attack.

To complicate matters, some common allergies may involve brain tissue, and this in turn may cause significant aberrations in mentation, feeling, and behavior which may mimic neurosis or other forms of psychological illness, or sometimes even structural neurological disease.[4,5,10,18]

Then, to make matters worse, some patients are basically emotionally unstable. Some are deeply neurotic. Some are psychotic enough to need constant psychiatric care—but wily enough to keep away from it.[1,15]

An allergist has to study all these kinds of patients from the viewpoint of his specialty. But sooner or later in the study and treatment of the emotional disorders of allergic patients, the allergist must make an important personal decision. He must determine for himself, after some careful soul-searching, whether or not he wishes to undertake the treatment of the emotional disorders of his patient—or, for that matter, whether or not he wishes to undertake the treatment of any other non-allergic aspect of his patient's health problems.

Every allergist does psychotherapy, whether or not he is aware of it. Much of what he may do is inherent in the patient-doctor relationship. In a sense, it is often unpremeditated, intuitive psychotherapy. When any special situation presents itself, he gives advice, suggestions, reassurance, supportive therapy which carries the patient along without disturbing the rhythm of his bustling office practice in allergy.

But the moment the allergist decides that he will add more formal types of psychotherapy to his usual practice of allergy, his customary mode of practicing will have to be altered, mainly because he will need to spend much more time with each patient he sees—or else, use some form of group therapy.[6,7,10,14,15,16] To introduce psychotherapy into everyday practice, the allergist will have to make the personal sacrifices entailed in learning whatever technique of psychotherapy he chooses to use. And he will need to become more easily aware of his own emotional reactions to the allergic patient, to the patient's life problems, and to his own emotional needs.

This means that we have many different classes of allergists, all of whom can contribute importantly to the welfare of allergic patients. The "pure" allergist is the man or woman whose psychotherapy is inherent in the patient-doctor relationship alone. Such psychotherapy is often unintentional, unconsciously directed, brief—and for many allergic patients, it is all the psychotherapy they need.

Next, we have those allergists who deliberately practice both allergy and psychotherapy. The type of psychotherapy used will depend on the doctor's special interest and training. Since psychotherapy is always an intensely personal type of treatment, we must recognize that one physician may be able to use one method effectively, whereas another equally capable physician may use an entirely different method equally well.

Then, we have the allergist whose main interest is in psychiatry, who quite incidentally also does allergy.

Lastly, we have the "pure" psychiatrist, whose main interest is in psychotherapy—but when his treatment is successful he may indirectly help some allergic patients by stabilizing their personalities and emotional behavior.

Once a practicing allergist has decided what kind of allergist he really wants to be, he will develop considerable peace of mind. He will find that as time goes along, he will be seeing in his practice the kind of patients he is interested in studying and treating. If he is desirous of limiting his practice exclusively to the allergic aspects of illness, he still renders a valuable service to his patients. Furthermore, he can always refer those patients needing psychiatric care to a co-operative psychiatrist whose treatment may be administered concomitantly with allergic therapy.

But I believe that increasing numbers of allergists prefer to do their own psychotherapy. They feel that as a result, nearly all their patients do better—and that some patients who could not have received benefits from allergic therapy alone do benefit when their psychological problems are treated simultaneously.[3]

Some allergists are really practicing psychiatrists. They see patients who have major psychiatric problems and minor allergic ones. These psychiatrists, wearing the label of "allergist" may be able to help mainly because their patients would avoid seeing any physician they knew to be a psychiatrist.

Let me give you some examples of problems which can arise in an allergist's practice which require knowledge of both allergy and psychiatry for their solution.

Case 1.—This thirty-six-year-old housewife consulted me because she thought she was allergic to housedust. Three days before seeing me, she had gone into her dusty attic to houseclean. Almost immediately, she began to have a stuffed-up, runny nose, watery eyes, sneezing and coughing. Several hours later, she developed a severe sinus headache not relieved by aspirin. All these symptoms decreased in intensity by the time she consulted me, but had not disappeared.

This superficial history suggested that she might be allergic to housedust, molds, or to some other inhalant material in her attic.

But further inquiry revealed that although she went into the attic with the intention of cleaning it up, her attention was diverted to letters tied together in neat bundles by blue ribbons. These had been lying in a big cardboard box. She had never seen these before, and since they were addressed to her husband, she saw no harm in reading a few. Her nose began to stuff up—not from the first moment of exposure to attic dust, but from the first moment she read the first letter. These letters were from her husband's former girl friend, and indicated the closeness of this former attachment.

As she told me about these passionate love letters, my patient's eyes watered, her nose ran, she sneezed; and she began complaining of severe headache. She resented her husband's former love affair, but even more his continuing emotional attachment, as shown by the fact that he had kept the letters as treasured mementos of his former mistress.

This woman's cure was brought about by her gaining insight into the nature of her own feelings, by her learning of the kinds of physiological reactions which strong emotions could engender, and by reassurance from her husband—who at first was annoyed that she had become so ill over a silly matter like his old love letters. He re-enforced his verbalizations of continuing affection for the patient by burning all the offending love letters. Then, at my suggestion, the patient went into the same dusty attic, gave it a thorough housecleaning, and had no recurrence of her "dust allergy."

*Case 2.**—This twenty-year-old woman had a real problem. She was being courted by a fat man and a thin man. Whenever she went out with the thin man, she was sure to break out in hives. She had no trouble when she dated the fat man. The solution to her problem seemed simple: eliminate the thin man from her life, and eliminate the hives. But this she was unwilling to do. She loved the thin man. And her worry was how to get rid of the hives without simultaneously getting rid of the thin man.

The allergist who saw her had a problem on his hands. A searching history indicated that very rarely the patient also had hives when she did not see the thin man. Skin testing revealed that she was intensely allergic to chocolate. Questioning revealed that the fat man who was courting her, fearing calories, always brought her flowers. But the thin man always brought her chocolates, which they ate during the evening.

Instead of subjecting this girl to unnecessary psychotherapy, the allergist solved a complex problem with the usual tools of his profession. The girl married the thin man. And it still is true today: no chocolate, no hives.

Case 3.—Mr. A., a forty-five-year-old man, consulted me saying the allergist who had been treating him "gave me up as a bad case, and told me my real trouble was that I was allergic to myself."

This patient had had for more than five years severe, nearly continuous nasal congestion which was so complete most of the time that he was unable to breathe through his nose. Privine, 6 to 8 drops in each nostril, would decongest his nasal mucous membranes sufficiently so that for ten to fifteen minutes thereafter he could with difficulty breathe through his nose.

His skin tests had been positive to early and late grasses, molds, dust and wool. For three years he had faithfully submitted to perennial injection treatment for these inhalant allergens without evidence of subjective or objective benefit. He had continued therapy mainly because his allergist assured him it might take several years to accomplish a cure. At home his bedroom was as dust-proof as was humanly possible to manage. His skin tests to food materials were negative.

Mr. A's wife and teen-aged daughter had become increasingly intolerant of his trouble. They disliked his irritability, his frequent use of nose drops even in the presence of company, the snorting noises he made trying to breathe through his nose. They felt he was doing nothing to help himself, and that if he only wanted to, he could control his irritability. He in turn resented bitterly the implication that he was a hypochondriac. He felt rejected, unwanted, and even unloved. In fact, his wife refused to have intercourse with him because he was such a "disgusting" person. This man's tension reflected itself in his work situation. He hated his boss, who was good to him, and wanted to quit his job. In moments of despair, he felt suicide would be better than trying to continue living in this way. He felt that he was doing everything a person could do to make likely a cure, and that doctors had failed him.

Examination showed that he was depressed. He cried during the interview, his

*Personal communication, Dr. George E. Rockwell.

nasal mucosa was a whitish-lilac color, swollen and boggy, with no discernible breathing space. He had considerable postnasal drip which he had not complained about. When I inquired about this, he said: "Sure, I have to spit all the time."

I asked him to stop using Privine and all other nasal decongestants for a month, and to keep a food-symptom-daily happenings-emotional self-analysis diary for me for a month.

He was no better at the end of a month. This ruled out the possibility that Privine could have been indirectly responsible for his excessive nasal congestion through a rebound engorgement phenomenon. Analysis of his notebook showed that although his symptoms were constant from day to day, whenever he was emotionally upset he would have extra amounts of milk and milk products.

My guess was that milk was one factor responsible for his nasal congestion. He was put on a milk-free diet. His nasal symptoms lessened within thirty-six hours, and disappeared within a week. When I saw him at the end of a month, he had no nasal symptoms. When I asked him to resume milk again, he reported that within fifteen minutes he had nasal congestion, which was complete within thirty minutes. He was then put on a milk-free diet, and was given instructions how to keep his diet high in protein, and calcium was prescribed for him.

As a result of prompt improvement in his nasal trouble, there was a remarkable improvement in his personality, and in his reactions to family, employer and friends. This reflected itself in improved relations at home with his wife and daughter. He lost his resentment, hostility and depressed feelings. In retrospect, Mr. A. had had a nasal allergy to milk, plus a violent psychological reaction to the discomfort of his allergic illness, and to the threatening actions of his wife and daughter.

This case illustrates a number of important facts. The first is that the basis of all psychotherapy of an allergic patient is a careful search for all allergenic agents. The correction of allergic illness alone is the most effective psychotherapy, since the patient loses all his subjective discomfort, objective signs of sickness, and can more easily understand why he reacted emotionally as he did to his illness, to his family and others. Supportive therapy is necessary during intervals when a doctor investigates the patient's problems and begins treatment. But usually complete recovery occurs when the patient is rendered symptom-free, and is given mainly an explanatory type of psychotherapy.

Mr. A. has continued to be well—and this is six years later. He has even developed enough clinical tolerance for milk so that a glass of this material once every two or three weeks causes no recurrence of symptoms.

SUMMARY AND CONCLUSIONS

Each allergist must decide for himself how much psychotherapy he wants to use in his practice. Even the allergist who limits himself to the psychotherapy inherent in the patient-doctor relationship is in a position to give many patients the aid they need. Only patients with complex emotional and psychological problems require more formal types of psychotherapy.

The most important aspect of the treatment of an allergic patient is a thoroughgoing search for the nature of allergens which cause his allergic disease. When this is discovered, it is often possible to ameliorate not only his allergic illness, but also secondary disturbances in his emotional and psychological behavior caused by his primary allergic illness.

Psychotherapy is often a useful aid in the management of allergic illness. But it is never a substitute for careful allergic work-up and treatment.

Nor, for that matter, are allergic study and therapy a substitute for the much-needed psychotherapy of a patient who has both primary allergic and concomitant primary psychiatric disorders.

A master allergist will always blend allergic therapy and psychotherapy to meet the realistic needs of his sick patient. This may mean that some allergic patients will receive mainly psychotherapy, and others, mainly allergic therapy. But above all it means that allergists will try to give their allergic patients whatever modalities of treatment they need to get well.

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THE USE OF AN ORALLY ADMINISTERED COMBINATION OF RAPID AND PROLONGED ACTING BRONCHODILATORS IN ASTHMATIC CHILDREN

A Clinical Study of "Nephenalin"*

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THERE IS an ever-present need for palatable medication giving both rapid and prolonged symptomatic relief of attacks of bronchial asthma in children. "Nephenalin" Pediatric* has been found effective for the treatment of asthma in adults,[4,7,9,11] and has now been prepared in the following formula for use in children:

N-Isopropylarterenol hydrochloride	5 mgm.
Theophylline	100 mgm.
Ephedrine Sulfate	18 mgm.
Phenobarbital	8 mgm.

The N-Isopropylarterenol is contained in the purple outer coating of the tablet for rapid sublingual absorption, the remaining ingredients are in the nucleus, which is swallowed after three to five minutes. N-Isopropylarterenol has been reported and confirmed as an effective rapid bronchodilator,[5,8,10] while the combination of oral ephedrine sulfate[8] and Theophyllin[10] is widely accepted as having less marked, but more prolonged, similar effects. The mild sedative action of phenobarbital has established its value in pediatric practice.

A clinical study of Nephenalin* "half-strength" in fifty asthmatic children has been carried out, most of the patients receiving the medicine as needed for a period of several weeks to one year. Table I summarizes the data on the clinical material. The patients' ages ranged from five to fourteen years. No younger children were included in the study because of the uncertainty of their ability to co-operate in using tablets as prescribed. However, this dosage has been administered to a few children as young as three years who were previously known to swallow tablets easily, who held them under the tongue satisfactorily. In most instances, the reaction to the first dose of Nephenalin given was observed by one of us, in order to insure proper use of the tablet, and to check on its effectiveness, and any immediate side effects. The clinical material consists of thirty-seven boys, thirteen girls, forty-six white, four colored. Duration of asthma varied from the first attack in one patient, to four-

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*This study was supported by a grant from Thomas Leeming & Co., Inc., who also supplied the "Nephenalin" Pediatric used.

TABLE I. SUMMARY OF CLINICAL MATERIAL

Patients—50 asthmatic children	
Diagnosis confirmed by history, physical examination, laboratory studies, skin tests, X-ray.	
Age—5 to 14 years	
Sex—13 females, 37 males	
Race—46 white, 4 colored	
Duration of asthma	minimum—1 attack
	maximum—14 years
	Average—3-6 years
Degree of asthma	Severe—40
	Moderate—9
	Mild—1

teen years in several of the older children. The average duration of asthma was three to six years. The degree of asthma was classified as mild in one child, moderate in thirteen, and severe in thirty-six children. Patients were selected because of availability for observation and follow up, for degree of co-operation and reliability of both parents and patient, and lastly in a small number because of our personal knowledge of their previous response to either or both, N-Isopropylaterenol theophylline, aminophylline, ephedrine, as well as to epinephrine.

"Nephenalin" Pediatric was effective in relieving asthma in thirty-three or sixty-six per cent of the fifty patients studied. In twenty-eight patients, complete relief of distressing dyspnea was obtained within fifteen minutes. In ten children, twenty to thirty minutes elapsed before they were comfortable. The duration of relief from one tablet was less than four hours in four, four to eighth ours in ten, and eight to twelve hours in thirteen, while six patients reported that one tablet completely abolished asthma. It is interesting to note that five of the latter were children with severe asthmatic attacks, which previously had required hypodermics or intravenous medication. This undoubtedly represents response to the N-Isopropylarterenol while the role of the remainder of the combination cannot be definitely established, although these children had not responded completely to previous treatment with N-Isopropylarterenol alone.

Among these thirty-three children, nineteen found "Nephenalin" Pediatric the most effective medication they had used for asthma. Fifteen of these children were severe asthmatics, who had been accustomed to using aminophylline rectally,[3] orally, and epinephrine or similar preparations in nebulizers. Our own observations of the clinical response in these children corroborated the parents impression after repeated use.

We found "Nephenalin" Pediatric completely ineffective in relieving acute asthma in eleven patients among the fifty, or 22 per cent. In four other children, the tablet was discontinued because of undesirable results. One child, age nine years, developed dizziness and palpitation although the asthma was relieved very effectively. Three had nausea after use. In two of these, the asthma was relieved and medication continued. In the third who was nauseated there was little benefit from the medication. One child objected to the color of the tablet and refused medication. In several others there was some objection to retaining medi-

TABLE II. EFFECTIVENESS OF "NEPHENALIN" PEDIATRIC IN ASTHMATIC CHILDREN

	Degree of Asthma			
		Severe	Moderate	Mild
Effective	33	28	4	1
Ineffective	11	6	5	
Inconclusive	3	3		
Inadequate report	3	3		
Total	50	40	9	1

TABLE III. TIME AND DURATION OF EFFECT OF "NEPHENALIN" PEDIATRIC IN ASTHMATIC CHILDREN

Asthma		Relief in Minutes				1 Dose	Duration in Hours		
		2	5	10-15	20-30		24	4-8	8-12
Severe	28	4	6	8	10	5	3	10	10
Moderate	4	4				1	1		2
Mild	1	1							1
Total	33	9	6	8	10	6	4	10	13

cation in the mouth. We subsequently noted that the tablets were not being swallowed quickly enough, and the objection was due to the bitterness of the inner nucleus. When this delay was rectified, these patients had no further objection to the medication, and found it effective. Table II summarizes the effectiveness of "Nephenalin" Pediatric in relation to severity of asthma.

In Table III, we have tabulated the type and duration of relief obtained from "Nephenalin" Pediatric in relation to the severity of asthma. It will be noted that the severity of symptoms has little relation to the duration of effective relief, but in the few patients with mild to moderate symptoms, immediate relief was obtained in all, while eighteen of twenty-eight severe asthmatics were relieved within fifteen minutes. Among the eleven patients for whom "Nephenalin" Pediatric offered no relief, the severity of asthma appeared to have no relation to effectiveness. It is our impression that these children, with one exception, are patients who are refractory to N-Isopropylarterenol, and in whom the other components are either ineffective because of habituation, or due to inadequate dosage by the oral route.

No deleterious effects of prolonged use of "Nephenalin" Pediatric were noted in blood, urine, weight, or appetite. There was no oral irritation, and no gastric irritation, except as noted in the two children with nausea.

The detailed studies on a smaller group of children will be reported in a subsequent paper in respect to physiologic effects of "Nephenalin" Pediatric* on vital capacity and oxygenation of the blood.

SUMMARY AND CONCLUSIONS

In summary, we conclude from our clinical trial for three weeks to one year of "Nephenalin" Pediatric in fifty children with moderately severe

to severe asthma that the combination gives effective relief in approximately 66 per cent, is relatively free from unpleasant side effects, there being only four who experienced any symptoms which made them reluctant to continue its use. No deleterious effects were noted in these children.

Obviously, the search for one medication which will always relieve asthma in everyone will continue until the perfect drug is found. Until then, it would seem that "Nephenalin" Pediatric may serve as a helpful new addition to our present medications.

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PRESCRIPTION WRITING

Careless prescription writing may give the patient the impression that there is careless examination and diagnosis. Whether the prescription be written in English or Latin, the important thing is to so write it that it will not be all Greek or Sanskrit to the pharmacist, and that he will know exactly what the prescriber wants.

There were many stories about the illegible handwriting of Horace Greeley, and we just heard a revised up-to-date version of one of these, but it had to do with a physician's prescription. It concerns a man who got a prescription which was described as having been written in the doctor's usual illegible scrawl. It seems the man recovered before he got around to having the prescription compounded, so he put it in his card case and forgot about it. Later he found a slip of paper in the card case and could not figure out what it was. So he tried it in different ways. For two years he used it as a railroad pass; several times he gained admission to Rockefeller Center Music Hall; it got him into the Yankee Stadium and an exclusive club; he used it as a note from his boss to the cashier for a raise in salary; and finally he brought it home and gave it to his daughter. She played it on the piano and won a scholarship in a conservatory of music.—From the *Pennsylvania Medical Journal*, February, 1952.

THE EVALUATION OF ORAL BRONCHODILATOR AGENTS IN PATIENTS WITH BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

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SINCE the report by Herrmann and Aynesworth[7] in 1937, the intravenous administration of aminophylline has become recognized as a valuable procedure for the relief of intractable bronchospasm. In a program to induce prolonged bronchial relaxation, Barach[1,2] employed the rectal instillation of aminophylline with equally good results. This method of administration had certain advantages since it could be carried out by the patient and was less likely to cause serious cardiovascular reactions. The intramuscular route proved impractical because of the intense pain and local reaction at the site of injection. The oral use of aminophylline has been limited by the high rate of occurrence of nausea and vomiting and considerable doubt as to its value has been expressed.[4] In studies by Barach,[3] and Bickerman and Beck,[5] it was noted that the clinical effectiveness of oral aminophylline was enhanced by ingestion in the fasting state.

Within recent years, there have been several reports on the use of synthetic sympathomimetic amines in relieving the bronchospasm of asthma and pulmonary emphysema.[6,10,11,13] Many of these agents were effective orally and sublingually as well as by inhalation and injection. The intention of this paper is to present an evaluation, clinically and by measurement of pulmonary function, of four oral bronchodilator preparations which were submitted to us for study. Because it is difficult to estimate relief of bronchospasm objectively, placebo tablets were also tested.

METHODS

Compound 753-1313* is a synthetic drug chemically related to ephedrine, epinephrine and aludrine with the formula 3,4-dihydroxyisopropylamino propiophenone hydrobromide. Pharmacologically, this compound appeared to be a relatively effective bronchodilator, readily absorbed on oral administration and causing no change in blood sugar or alteration in central nervous system stimulation.[8]

A total of eighty-two patients with clinical evidence of bronchospasm were given a week's clinical trial with Compound 1313. The average daily

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*Prepared and supplied by the Department of Pharmacology of Sharp and Dohme, Glenolden, Pa.

dose ranged between 100 and 200 mg in divided doses, usually given two or three times a day on an empty stomach. The effect of this medication was compared to the relief obtained with oral aminophylline or inhaled 2.25 per cent racemic epinephrine (Vaponefrin** N.R.). Relief was graded according to (1) decrease of wheeze, (2) diminution of cough and (3) decrease in dyspnea associated with improvement in exercise tolerance. Graphic tracings of vital capacity and maximum breathing capacity were recorded on a Benedict-Roth spirometer in seventeen members of this group, thirteen of whom had bronchial asthma and four with pulmonary emphysema of the bronchospastic type. Immediately following a control study, each subject received 75 mg of Compound 1313 in the fasting state. Pulmonary function studies were repeated one hour after ingestion of the drug. Each patient then inhaled 0.3 cc of Vaponefrin and after an interval of fifteen minutes the tracings were repeated.

Nephenalin† (N.R.) is a drug mixture composed of an outer coating containing 10 mg of N-isopropyl arterenol hydrochloride which is absorbed sublingually, with the remainder of the tablet consisting of theophylline 120 mg, ephedrine sulfate 25 mg, and phenobarbital 8 mg for absorption via the alimentary tract. Ninety-four patients were given a week's trial of this drug. The average dose ranged between two and four tablets daily and each patient was instructed to permit the tablet to dissolve slowly under his tongue for approximately five minutes or until a bitter taste was perceived, and then to swallow the remainder of the tablet. Pulmonary function studies with determinations of the vital capacity and maximum breathing capacity were performed on thirty-six of the ninety-four subjects, and in twenty-four members of this group, electrocardiograms were obtained before and one hour after, administration of Nephenalin.

Dainite‡ (N.R.) is a drug consisting of two tablets of differing composition. The "Day" tablet contains aminophylline 200 mg, ephedrine hydrochloride 15 mg, aluminum hydroxide 160 mg, ethyl aminobenzoate 15 mg and sodium pentobarbital 15 mg. In the "Night" tablet ephedrine is omitted, aminophylline is increased from 200 to 250 mg, sodium pentobarbital from 15 to 30 mg, and 25 mg of phenobarbital are added. A total of 155 clinicial trials of one or more weeks' duration were obtained with Dainite; the customary dose being one "Day" tablet on arising and a "Night" tablet on retiring. Pulmonary function studies were performed on nineteen patients after the "Day" tablet and on eleven subjects after the "Night" tablet in a manner similar to the procedure described above.

Cardalin‡ (N.R.) contains 300 mg of aminophylline as the chief therapeutic constituent. To this has been added aluminum hydroxide 160 mg and ethyl aminobenzoate 30 mg. Sixty-four patients have received a clinical trial with this drug with the average dose ranging between two to three

**Supplied by Vaponefrin Company, Upper Darby, Pa.
†Supplied by Thomas Leeming and Company, New York, N. Y.
‡Supplied by Irwin, Neisler and Company, Decatur, Illinois.

TABLE I. EFFECT OF ORAL BRONCHODILATORS ON THE VENTILATORY FUNCTION OF PATIENTS WITH BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

Drug	No. of Cases	Vital Capacity			Maximum Breathing Capacity		
		Mean % Change	S. D.	t value	Mean % Change	S. D.	t value
1313	17	− 0.96	±19.34	0.21	+ 6.35	±24.31	1.08
Nephenalin	36	+10.28	±13.64	4.52	+15.75	±30.07	3.01
Day Tablet	19	+ 9.70	±12.04	3.50	+12.60	±16.90	3.20
Night Tablet	11	+ 9.38	±13.84	2.25	+ 8.86	±16.35	1.80
Cardalin	11	+12.51	±10.90	3.80	+22.05	±24.95	2.93

tablets daily. Eleven patients in this series had pulmonary function studies before and one hour after administration of Cardalin.

The blood plasma levels of theophylline were determined in nine patients by the method described by Truitt, et al.[14] For a period of twenty-four hours prior to the test, xanthine-containing foods such as coffee, tea and cola beverages were omitted from the diet. After a control blood specimen had been obtained and the Cardalin administered, blood samples were collected at one-, three-, five- and seven-hour intervals, and the plasma analyzed for theophylline content. Five of the subjects received a single dose of Cardalin containing 300 mg of aminophylline while the other four received two tablets containing 600 mg.

Placebo tablets, similar in appearance to the individual drugs tested, were administered to ten patients whose pulmonary function studies were performed.

RESULTS

Following a week's clinical trial with Compound 1313, twenty-three of the eighty-two patients reported slight to moderate improvement in asthmatic symptoms. The remaining fifty-nine subjects obtained little or no relief. Wheeze and cough were not materially altered and the sputum showed no change in character. One patient in this series reported a slight tremor and increased perspiration lasting fifteen minutes following ingestion of the drug. A second patient who had experienced moderate relief of asthma developed a generalized macular eruption during the first week of administration of Compound 1313 which disappeared on withdrawal of medication. A statistical analysis of the pulmonary function studies performed on seventeen patients in this series revealed insignificant changes of —0.96 and +6.35 per cent in the mean vital capacity and maximum breathing capacity following administration of the drug (Table I, Figs. 1, 2) as compared with the highly significant increases in ventilatory function following the inhalation of Vaponefrin.

Fifteen of the ninety-four patients receiving Nephenalin obtained marked relief of asthmatic symptoms during the week of administration; thirty-four reported moderate improvement while the remaining forty-five observed little or no effect of the preparation on wheeze, cough and dyspnea.

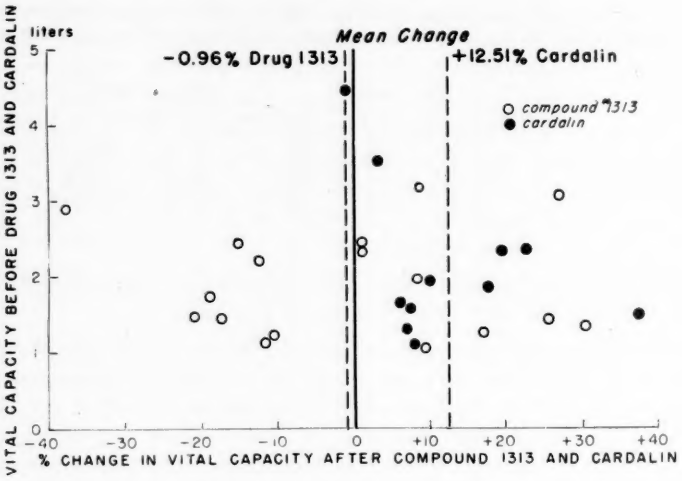

Fig. 1. The per cent change in Vital Capacity is illustrated in seventeen subjects one hour after Compound 1313, and in eleven patients after Cardalin.

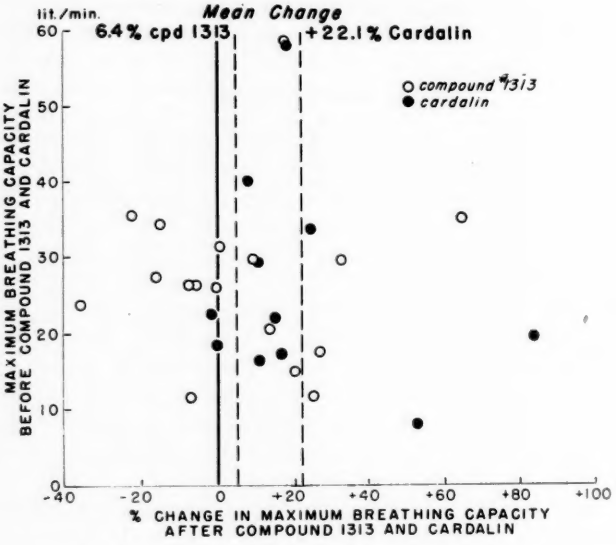

Fig. 2. The per cent change in Maximum Breathing Capacity is illustrated in the same individuals one hour after Compound 1313 or Cardalin.

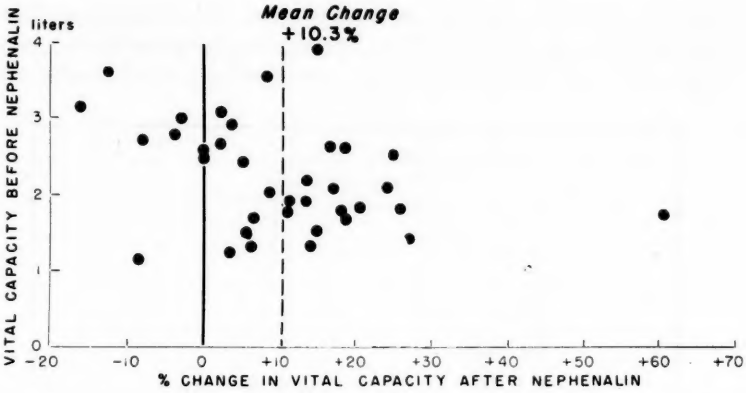

Fig. 3. The effect of Nephenalin on the Vital Capacities of thirty-six patients is expressed as the per cent change from the control level.

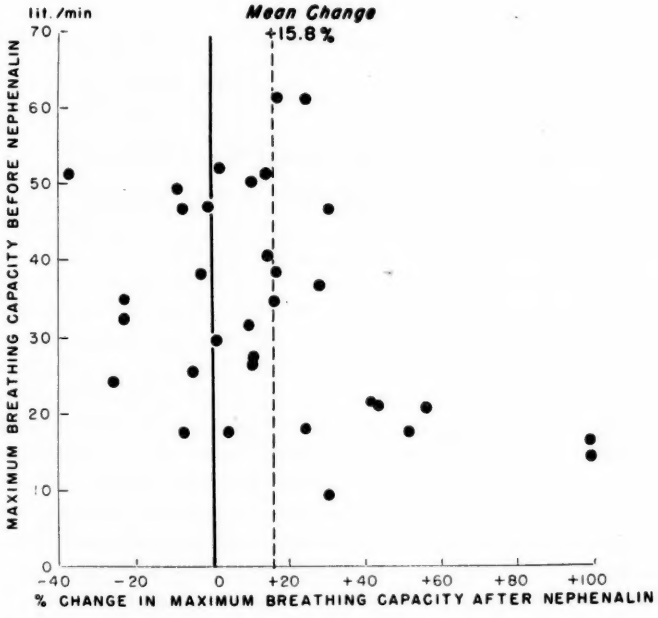

Fig. 4. The effect of Nephenalin on the Maximum Breathing Capacities is illustrated.

Side effects were encountered in thirteen patients, ten of whom experienced palpitation, dizziness and headache resulting from sympathomimetic stimulation. Two patients complained of nausea and an elderly patient with

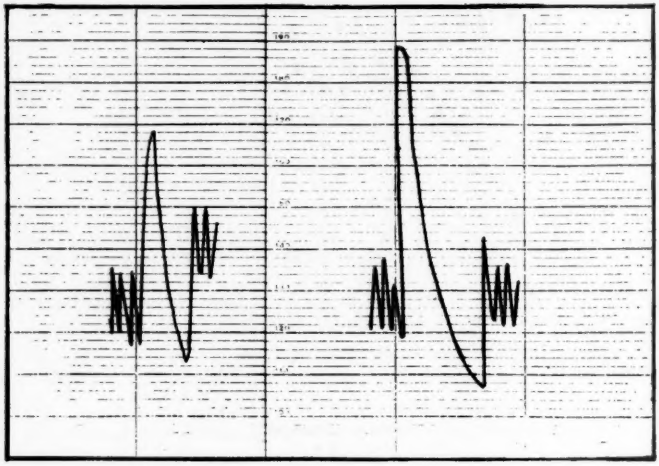

Fig. 5. Spirogram illustrating the effect of "Day" tablet on the vital capacity in a patient with bronchial asthma.

obstructive emphysema developed urinary retention after the first day of therapy. Further questioning revealed that ephedrine had caused urinary block on previous occasions.

Electrocardiograms performed on twenty-four patients in this series revealed no significant changes in the tracings taken one hour after administration of Nephenalin when compared with the control tracing. A slight increase in rate occurred averaging four beats per minute. In ten additional studies performed on patients who had received a tablet containing 13 mg of N-isopropyl arterenol in the outer coating, sinus tachycardia was present in five. A sixth patient exhibited multiple premature ventricular complexes. An analysis of the effect of Nephenalin on ventilatory function in the thirty-six patients tested is presented in Table I, Figs. 3, 4. A mean increase of 10.28 per cent and 15.75 per cent occurred in vital capacity and maximum breathing capacity, respectively. The t value calculated for each test denotes a high degree of significance with a probability of less than 0.001 that these could be chance occurrences.

An excellent clinical response was obtained in seventy-five of 155 patients given the Dainite preparation. An additional thirty-seven patients reported moderate improvement while forty-three patients experienced little

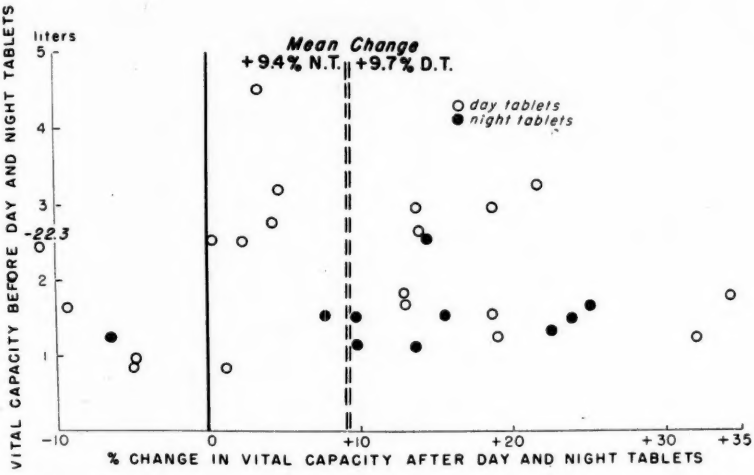

Fig. 6. The changes in Vital Capacity one hour after Dainite are plotted in a combined group of thirty patients.

or no relief of asthma during the week's course of therapy. A total of sixteen patients in this series reported side reactions of a sympathomimetic nature consisting of dizziness, weakness and palpitation. Three subjects complained of nausea and twenty-two noticed increased drowsiness and slight impairment in mental alertness.

Following a single dose of the "Day" tablet, the mean vital capacity increased 9.7 per cent and the maximum breathing capacity rose 12.6 per cent in the nineteen patients tested. The effect of "Day" tablet on the vital capacity of a patient with bronchial asthma is illustrated in Fig. 5. Eleven patients were studied following a "Night" tablet and showed a mean increase of 9.38 and 8.86 per cent in the vital capacity and maximum breathing capacity, respectively. Statistical analysis of the data is presented in Table I and Figs. 6, 7. The t values calculated for "Day" tablet were highly significant while the "Night" tablet data was of borderline significance.

Of the sixty-four patients treated with Cardalin, thirty-one reported excellent results; moderate improvement occurred in sixteen, and no effect was noted by seventeen patients. Side reactions were minimal with seven patients complaining of nausea; emesis occurred in three as long as four hours after ingestion of the drug. Five subjects experienced palpitations

associated with slight excitation and insomnia. The ventilatory function studies showed significant increases of 12.51 per cent and 22.05 per cent in the mean vital capacity and maximum breathing capacity of the eleven

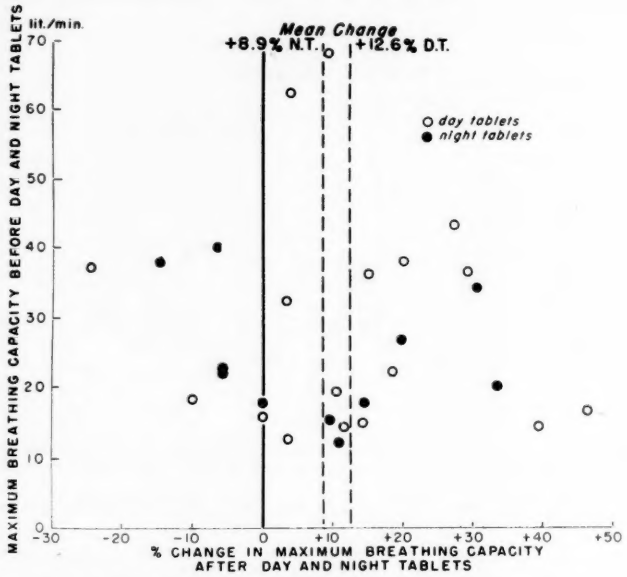

Fig. 7. The effect of Dainite on the Maximum Breathing Capacities is shown as per cent change from the control level.

TABLE II. PLASMA LEVELS OF THEOPHYLLINE AFTER ORAL ADMINISTRATION OF CARDALIN

Dose (mgm.)	Case	Hematocrit	Plasma Levels (M/100 cc)			
			1 hour	3 hours	5 hours	7 hours
300	1	47	580	760	630	550
300	2	52	900	790	350	390
300	3	39	420	900	850	600
300	4	37	0	760	600	500
300	5	43	760	980	650	560
Mean			530	840	616	520
600	1	52	1360	980	680	540
600	2	44	940	1960	1580	1400
600	3	45	1280	1100	520	780
600	4	35	1200	1140	740	580
Mean			1195	1295	880	825

patients tested (Table I). The results on each subject were plotted on the same scale as the data for Compound 1313. (Figs. 1, 2.)

The plasma theophylline levels following one and two tablets of Cardalin

are reported in Table II, Fig. 8. Appreciable levels were present after seven hours following administration of the drug with the peak occurring at the third hour; 840 micrograms per cent with the 300 mg dose and 1295

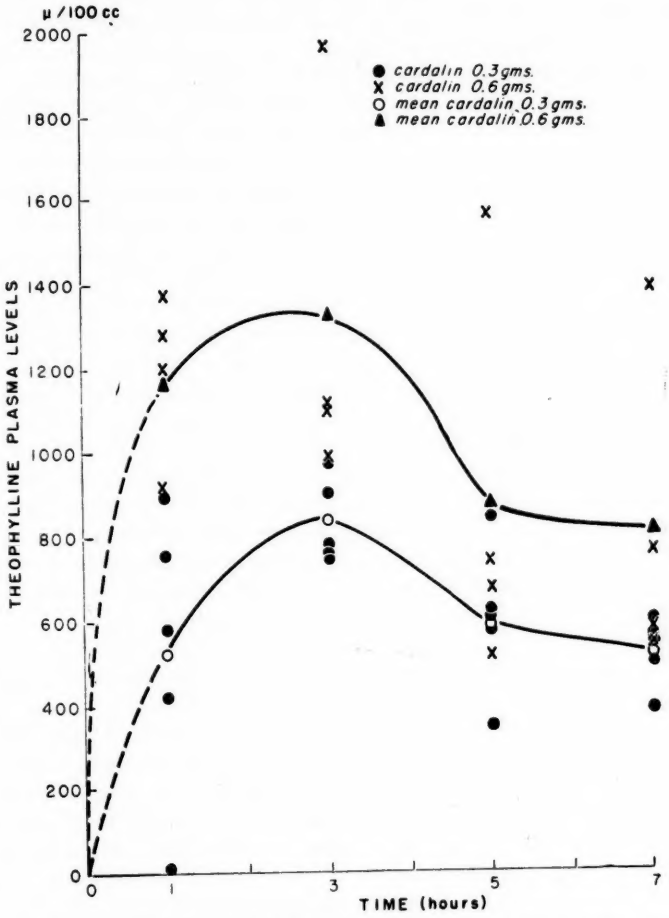

Fig. 8. The plasma theophylline levels determined for a seven-hour period following the ingestion of 300 and 600 mg of Cardalin are graphed.

micrograms per cent with the 600 mg dose. Only one subject receiving a single tablet had no recoverable theophylline at the one-hour sampling period.

A placebo tablet administered orally to ten patients showed a mean

change in vital capacity of —4.5 per cent and in maximum breathing capacity of +5.8 per cent. These results were reported in detail elsewhere.[5]

COMMENT

In reviewing the clinical data as well as the effect of these oral bronchodilator drugs on the vital capacity and maximum breathing capacity of patients with bronchial asthma and pulmonary emphysema, it was apparent that Compound 1313 was as ineffective in relieving bronchospasm as the placebo tablets. Nephenalin, Dainite and Cardalin appeared to give moderate to excellent relief of mild asthma in the majority of the subjects in this study. These drugs afforded little or no therapeutic benefit in the severe bronchospastic states and this was especially evident in patients with status asthmaticus. Nephenalin, by virtue of the sublingual absorption of N-isopropyl arterenol, had a more rapid onset of bronchodilator activity but the degree of persisting benefit was considerably shorter than with Dainite or Cardalin, necessitating a dosage interval of four to six hours, whereas Dainite and Cardalin could be given at eight- to twelve-hour intervals.

Ventilatory function studies following a single dose of Nephenalin, Dainite or Cardalin showed a small but significant degree of improvement in vital capacity and maximum breathing capacity. In all of the subjects treated with these oral bronchodilator agents, the inhalation of Vaponefrin aerosol resulted in an increase in the clinical relief of bronchospasm. This was corroborated by a further mean rise of 10 to 15 per cent in vital capacity and maximum breathing capacity following the inhalation of 0.3 cc of Vaponefrin indicating that additional bronchodilatation and bronchovasoconstriction is accomplished by nebulized epinephrin.

Although the excellent bronchodilator activity of aminophylline when given intravenously has been well documented, the oral route of administration has been impractical because of the high incidence of nausea and vomiting associated with doses exceeding 200 mg. Enteric coating, while materially reducing the incidence of these side effects, has resulted in impaired absorption. Waxler and Schack[15] found wide variations in the theophylline blood levels after oral ingestion of enteric coated aminophylline tablets with many of the subjects failing to demonstrate any detectable blood levels. The administration of uncoated tablets resulted in a rapid appearance of theophylline in the blood as early as fifteen minutes after ingestion with levels persisting for nine hours. In attempting to mitigate gastrointestinal intolerance to aminophylline and not interfere with absorption, aminophylline was combined with aluminum hydroxide and ethyl aminobenzoate. Patients were able to tolerate 300 mg and in some instances 600 mg of aminophylline in this combination with relatively few side effects.

In view of the excellent clinical effect of intravenously administered aminophylline, it is apparent that relief of bronchospasm depends on the blood levels of theophylline achieved with the various routes of administra-

tion. Truitt and his co-workers[14] determined that the effective blood level of theophylline necessary for significant diuretic activity was 0.5 mg per cent. These levels were attained or exceeded by 500 mg of aminophylline given intravenously, by retention enema and with oral uncoated tablets. No comparable study correlating bronchodilator activity with the theophylline blood levels has been performed. Protection studies performed by Segal et al[12] demonstrated that 0.4 gm of oral aminophylline gave relatively low degrees of protection against bronchospasm induced by histamine and methacholine as compared with the intravenous and rectal routes, and furthermore, this was observed after a delay of approximately two hours after ingestion. Schack and Waxler[9] determined blood theophylline levels in rabbits, mice and humans by a spectrophotometric method and found that the theophylline content was restricted to the plasma of the circulating blood and was very loosely bound to the plasma proteins. The mean blood theophylline levels calculated from the plasma content and hematocrit exceeded 0.5 mg per cent in the four subjects tested with 600 mg of Cardalin for the seven-hour collection period. A comparison of these levels with the data obtained by Truitt, et al,[14] employing 500 mg of aminophylline given intravenously, indicates that 600 mg of oral Cardalin yielded a lower theophylline blood level at the one-hour sampling period, but the mean levels at the third- fifth- and seventh-hour periods exceeded the values obtained with intravenous aminophylline. Three hundred milligrams of Cardalin resulted in a mean peak blood level of 0.47 mg per cent three hours after ingestion. No comparison between the change in ventilatory function and the blood theophylline level was attempted in the present study.

SUMMARY

The clinical effectiveness of four bronchodilator drugs was studied in patients with bronchial asthma and pulmonary emphysema.

Compound 1313 (3,4-dihydroxyisopropylamino propiophenone hydrobromide) proved ineffective in the majority of the eighty-two patients given a week's clinical trial. No significant changes in vital capacity or maximum breathing capacity were demonstrated either in this drug or in the placebo.

Moderate to excellent clinical relief of bronchospasm occurred in 52 per cent of the ninety-four patients taking Nephenalin, N.R. (N-isopropyl arterenol hydrochloride, theophylline, ephedrine sulfate and phenobarbital); 72 per cent of 155 patients on Dainite, N.R. (ephedrine hydrochloride, aminophylline, aluminum hydroxide, ethyl aminobenzoate, sodium pentobarbital); and 75 per cent of sixty-four patients receiving Cardalin, N.R. (aminophylline, aluminum hydroxide and ethyl aminobenzoate). Ventilatory function studies showed a mean rise of approximately 10 per cent in the vital capacities and 10 to 20 per cent in the maximum breathing capacities following the administration of each of these three preparations. Excellent clinical results were obtained in patients with mild to moderate

bronchospasm; but these drugs failed to relieve the symptoms of severe intractable asthma.

The incidence of adverse side reactions to all four of the groups of drugs tested was minimal. Cardalin, in doses as high as 600 mg, appeared to be well tolerated with a comparatively low incidence of gastrointestinal disturbance.

The plasma theophylline levels on 300 and 600 mg of Cardalin revealed appreciable concentrations of theophylline in the circulating blood as long as seven hours after administration.

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THE RELIEF OF BRONCHIAL ASTHMA WITH ORAL KHELLIN

RALPH M. MULLIGAN, M.D., F.A.C.A.
Reading, Pennsylvania

IN 1947, Anrep et al,[1] noting that Samaan[7] had shown khellin to be a dilator of respiratory passages, reported that a single intramuscular injection of 200 to 300 mg of khellin gave complete and prolonged relief to forty-one of forty-five patients with severe bronchial asthma. Anrep also noted that daily administration of khellin by mouth reduced the number and severity of the attacks. In 1949, Major[5] reported that the daily oral administration of 400 mg of khellin provided rapid and lasting relief; Kenawy et al,[4] on the other hand, reported that only mild asthmatic attacks were relieved by 100 to 250 mg of khellin given orally. Rosenman et al,[6] who used khellin intramuscularly, noted that although prompt and occasionally complete relief was effected the relief was not lasting. Derbes et al,[3] in 1951, reported that fourteen of twenty-five patients experienced good or excellent relief of symptoms while taking 100 mg of khellin daily by mouth. Braun and Eilender,[2] using khellin in the form of an aerosol spray, produced clinical improvement and an increase in vital capacity in all of ten patients who had acute bronchial asthma.

MATERIAL AND METHOD

Thirty patients with long-standing nonseasonal asthma were selected for this study. Nineteen were women from twenty-five to sixty-six years; eleven were men from thirty-nine to sixty-three years. In twenty-five the asthma was chronic, with numerous (five to fifteen a year) severe paroxysms in fifteen of these and moderate paroxysms in ten. All but three were emotionally stable people in whose bronchial asthma psychogenic factors did not appear to play a large part. In seven of the patients, the pattern of cold-bronchitis-paroxysmal asthma was apparent. In eight there were concomitant disorders often associated with bronchial asthma: eight had significant emphysema; three had severe allergic rhinitis; one had nasal polyps; one had pneumonoconiosis.

Each patient was given a bottle, marked only with a code number, containing 40-mg tablets of Eskel.* Each was told that the bottle contained a new drug being investigated for use in asthma, and was told that we would later ask for an opinion of the effectiveness of the drug, as well as a report of any side effects (dizziness, insomnia, rashes, headache, nausea, vomiting, et cetera) that the drug might produce. In these preliminary instructions, and in later discussions with the patients, we were careful to

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*Product of Smith, Kline & French Laboratories, Philadelphia.

place no emphasis on nausea and vomiting as the two side effects most likely to occur. Nineteen of the patients took one 40-mg tablet twice a day, one tablet after breakfast, the other after their evening meal; three took three tablets a day after meals; and eight took two tablets a day during acute attacks only. Unless otherwise noted below, all of the patients described here have taken Eskel for at least six months, either to reduce the severity of acute attacks or to relieve chronic asthma, or both.

At the same time that they were given a supply of Eskel tablets, eleven patients were given a supply of placebo tablets. These were identical in appearance and taste to the Eskel tablets, differing only in the code number that identified each drug. These eleven patients were told that two drugs were being investigated in bronchial asthma and that we would later welcome a comparison of the effectiveness and acceptability of the two. Ten of them were told to take two or three tablets of Eskel on one day, to take the same dose of placebo on the next, to resume taking Eskel on the third day, and so on until their supply of the two drugs was exhausted. The other patient was told to take two or three tablets of Eskel a day for one week, then two or three tablets of the placebo a day for the next week, and so on.

During subsequent visits the blood pressure of each patient was measured, and each was asked for information (if he had not already volunteered it) on the side effects that he had noted. The patients were also asked to evaluate the effectiveness of the drug in relieving chronic asthma or in relieving the severity of acute attacks. They were asked to do this by comparing the speed, duration, and degree of relief to the same features of relief that they had previously experienced when taking epinephrine by injection or inhalation, aminophyllin, ephedrine, or an ephedrine-aminophyllin-sedative combination.

By comparing the number of home and office visits required in the period of Eskel therapy to the number required in a similar period before Eskel therapy, we were able to arrive at a rough evaluation of the lessening of the number (or, more probably, of the lessening of the severity) of acute attacks. Thus, from the information obtained from the patient and from a study of the frequency of emergency calls, we obtained an impression that the Eskel therapy was good, fair, or poor.

RESULTS

Based on these methods of evaluation, we arrived at the impression that of the thirty patients: good results were obtained in twenty-two, fair results in four, and poor results in four. In the twenty-two in whom good results were obtained, Eskel succeeded in controlling entirely the asthma of fourteen. In the other eight, additional palliative therapy became necessary. All twenty-two reduced their number of trips to our office by 50 to 75 per cent, based on the number in the six months' period before therapy, and reduced the number of emergency house calls by an even larger per-

centage. All twenty-two commented that the drug had proved more helpful than, or just as helpful as, drugs that they had used previously.

The four patients in whom Eskel produced fair results showed a slight lessening of the number and severity of their attacks and maintained that the drug was helpful. However, when it became obvious that the degree of relief was but fair, additional palliative therapy was instituted. Of the four in whom the efficacy of Eskel was rated as poor, one had pneumonoconiosis; one had hypertensive heart disease and stopped taking the drug because of nausea and vomiting; and two showed no discernible results, nor any side effects.

Of special interest was the remarkable lack of effect produced by the placebo. Without exception, the patients who took it stated that it was of no help to them. Remarkable, too, was the fact these patients insisted that the placebo had produced no side effects; whereas at times the Eskel had. This lack of effect can best be explained by the fact that, following the instructions that had been given them, the patients discontinued taking the placebo as soon as they had discovered that one drug was better than the other. Had the difference in action been less distinct and had they continued their comparison of the two drugs, it is possible that they would have ascribed certain side effects to the placebo.

As for side effects, seventeen of the patients reported that Eskel had nauseated them at least slightly; five of these reported that it had made them vomit once or twice during the six-month period. As has been mentioned, one patient with hypertensive heart disease was asked to stop taking the drug when he reported that it had made him vomit. Other side effects were reported, such as anorexia, headache, insomnia, and pruritus; but these were reported so infrequently that their relationship to Eskel could scarcely be demonstrated. One patient, an intelligent and co-operative sixty-three-year-old woman who experienced good relief from asthma every time she took Eskel, also experienced "a far-away feeling" that made it impossible for her to continue taking Eskel orally. Because of her eagerness to continue, she was given 40 mg Eskel, twice daily, in suppository form, but again, although her asthma was relieved, she experienced the same vague but debilitating effect that had forced the discontinuance of oral therapy. The Eskel suppositories were then supplied to three other patients, two of whom reported excellent results.

CONCLUSION

Of thirty patients with long-standing, nonseasonal asthma, twenty-two obtained good relief from oral Eskel, four obtained fair relief, four obtained no relief. A placebo administered to eleven of the patients produced neither ill nor beneficial effects. Seventeen of the patients reported that the drug nauseated them somewhat, but this nausea was not severe enough, except in one case, to prompt them to discontinue the therapy. One reported a debilitating langour following the administration of Eskel,

either in oral or suppository form. The principal conclusion of this study, that khellin is effective in relieving the symptoms of asthma, does not differ substantially from the conclusions of earlier published reports. Rather, the difference lies in the size of the effective dose and in the striking lack of effectiveness of a placebo.

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18 North Eleventh Street

NEW A.C.A. MEMBERS

At the recent meeting of the American College of Allergists in Chicago, the Board of Regents elected the following applicants to Associate Fellowship:

Dr. David Leonard Lieberman
West Main Street
Chester, Connecticut

Dr. Clarence Y. Sugihara
1010 South King Street
Honolulu 14, Hawaii

Dr. Marcus Kellogg Mookerjee
3872 North Green Bay Avenue
Milwaukee 6, Wisconsin

Dr. Ly Werner
25 Medical Arts Square
Albuquerque, New Mexico

At the Board Meeting, the following members were promoted to Active Fellowship:

Dr. William McPherson Fitzhugh, Jr.
384 Post Street
San Francisco, California

Dr. Robert J. Peirce
513 Chevy Chase
Mansfield, Ohio

The College extends warmest welcome and best wishes to these new members.

PERSONALITY CHANGES INDUCED IN CHILDREN BY THE USE OF CERTAIN ANTIHISTAMINIC DRUGS

NATHAN SCHAFFER, M.D., F.A.C.A.

East Orange, New Jersey

MANY authors have described the unfavorable side reactions of the antihistaminic drugs over the past three years, but no stress has been placed on the unfavorable personality changes which may be encountered in children with prolonged usage of these drugs, either alone or in combination with other drugs. This report will attempt to analyze the effects of certain antihistaminic drugs on twenty-three children who have taken some form of the drug for periods of from one month to two years.

These children have been treated for various allergic states; seasonal and non-seasonal vasomotor rhinitis, asthma, and eczema. Before therapy, all of these children had been well-adjusted and had fitted into the family pattern without abnormal difficulty. In many instances the subsequent problem of personality change was brought to the attention of the parents by school teachers who noted a sudden or gradual lack of interest in school work, temper outbursts, crying spells, or antagonism.

Medical examination revealed an apprehensive or antagonistic child. Careful questioning in each case established the onset of these symptoms after the start of the antihistaminic therapy.

Table I indicates which antihistaminic drug was taken, for what condition the drug was given, and the personality changes which subsequently developed. The antihistaminic drugs were employed only in the recommended doses.

In all cases, symptoms of the personality changes disappeared within two or three days after the offending drug was stopped. In those asthma cases where the antihistamine had been given with ephedrine sulphate and aminophylline, these drugs were given separately without producing similar personality changes, but when the designated antihistamines were again prescribed, the behavior symptoms reappeared.

CONCLUSIONS

1. Twenty-three cases of altered personality in children due to certain antihistamines are reported.
2. With cessation of the offending antihistamine drug, there was a complete reversal to the normal state in two to three days.

Presented at the Ninth Annual Congress of The American College of Allergists, April 27-29, 1953, Chicago, Illinois.

Approved for publication on November 21, 1952.

TABLE I

Patient	Sex	Age	Symptoms for which given	Drug used	Personality changes
S.W.	F	9	Seasonal vasomotor rhinitis	Tripelennamine[3] Hydrochloride	Crying, irritability
S.E.	F	4	Eczema	Diphenhydramine[4]	Irritability, disobedient, weepy, and perverse
D.W.	M	4½	Asthma and vasomotor rhinitis, non-seasonal	Diphenhydramine[1]	Irritability, weepy, perverse
R.W.	M	6	Asthma and seasonal vasomotor rhinitis	Tripelennamine[3]	Irritable and weepy
S.S.	M	5	Asthma and non-seasonal vasomotor rhinitis	Diphenhydramine[4] Tripelennamine[3]	Irritable, weepy
J.S.	M	4	Asthma; seasonal vasomotor rhinitis	Tripelennamine[3]	Weepy, disobedient, mopey, irritable, indifferent
G.P.	M	3	Asthma; non-seasonal vasomotor rhinitis	Tripelennamine[3]	Cantankerous, disobedient
J.H.	F	7	Asthma; seasonal vasomotor rhinitis	Diphenhydramine[1]	Irritable, weepy, loss of appetite
B.B.	F	6	Asthma; non-seasonal vasomotor rhinitis	Diphenhydramine[1]	Irritable, weepy
R.W.	M	5	Asthma; perennial vasomotor rhinitis	Tripelennamine[3] Diphenhydramine[1]	Irritable, weepy, antagonistic
D.S.	M	6	Asthma; seasonal vasomotor rhinitis	Tripelennamine[3] Diphenhydramine[1]	Irritable, loss of appetite, antagonistic
R.M.	M	8	Asthma; seasonal vasomotor rhinitis	Diphenhydramine[1]	Antagonistic, weepy, irritable
C.M.	F	4	Perrenial vasomotor rhinitis	Diphenhydramine[1]	Irritable, weepy
P.K.	M	5	Asthma	Diphenhydramine[4]	Weepy, loss of appetite
K.K.	F	10	Asthma and Eczema	Diphenhydramine[1] Tripelennamine[3]	Irritable, weepy
C.C.	F	7	Asthma; seasonal vasomotor rhinitis	Diphenhydramine[1]	Irritable, antagonistic, loss of appetite
M.B.	F	8	Asthma	Tripelennamine[3] Pyrilamine Maleate[2] Diphenhydramine[1]	Weepy, antagonistic, irritable, loss of appetite
B.B.	M	4	Asthma; seasonal vasomotor rhinitis	Pyrilamine Maleate[2] Diphenhydramine[1]	Weepy, irritable
J.A.	M	2	Asthma	Tripelennamine[3]	Weepy, irritable, loss of appetite
G.A.	F	5	Asthma	Diphenhydramine[1] Tripelennamine[3]	Irritable, whiney
E.W.	F	7	Eczema	Diphenhydramine[4] Tripelennamine[3] Pyrilamine Maleate[2]	Weepy, irritable, loss of appetite
V.A.	M	2	Asthma	Diphenhydramine[1]	Irritable
A.A.	F	4	Asthma	Diphenhydramine[1]	Irritable, obstinate, weepy

1. Diphenhydramine and Aminophylline (Hydryllin, Searle & Co.)
2. Pyrilamine Maleate (Neo-Antergan, Merck & Co.)
3. Tripelennamine Hydrochloride (Pyribenzamine, HCL, Ciba)
4. Diphenhydramine Hydrochloride (Benadryl, Parke Davis & Co.)

98 South Munn Ave.

A NEW SUBLINGUAL THERAPY FOR BRONCHIAL ASTHMA

ELIZABETH B. BROWN, M.D.
Philadelphia, Pennsylvania

A PATIENT with bronchial asthma in the throes of an acute paroxysmal attack is concerned primarily with getting rapid and adequate relief from his symptoms. A physician is not always available to administer the necessary measures for relief; therefore a medication which will produce the desired effect with the greatest ease of administration is desirable.

For many years parenteral epinephrine has been the standard therapy for the relief of acute attacks of asthma. This procedure is not practical from the patients' standpoint since they must be taught self administration of parenteral epinephrine, a technique which is hazardous in the hands of many patients. Inhalation of epinephrine and other drugs has proved to be of some value, but this requires constant availability of a nebulizer. Of even greater importance is the danger of overdosage.

Through the co-operative efforts of pharmacologists and pharmaceutical research chemists, a number of compounds have been made available for clinical trial, and several have shown promise of clinical effectiveness. Several years ago isopropyl arterenol was introduced into this country for the treatment of asthma. This compound was the result of an attempt to find a drug with the bronchodilator capacities of epinephrine but without epinephrine side effects. Chemically, it is similar to epinephrine; pharmacologically, it has greater bronchodilating action, but unfortunately it produces effects on the heart paralleling the parent compound.[3,2] The side effects most frequently encountered are tachycardia and nervousness, which develop as a result of the stimulating effect and are transitory. However, the tachycardia can be very alarming to the patient if not forewarned of this action. It is obviously poor practice to have to give such warning to susceptible patients.

As a result of the adverse clinical experiences with isopropyl arterenol, pharmacologists and pharmaceutical chemists carried on further investigations to try to improve the compound or to combine it with some other drug which would enhance its therapeutic effect and would reduce or even eliminate its side effects. A preparation would be interesting clinically which could be given by the sublingual route, which would effect rapid relief and which would be practically free from all side effects produced by isopropyl arterenol alone. It was decided to seek a compound which would activate the therapeutic effects of isopropyl arterenol and at the same time counteract or modify its action on the heart.

Many nicotinamides have been studied and a number of them have been

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Dr. Brown is an Associate Fellow of the American College of Allergists.

found to possess potent antispasmodic properties. The benzyl derivative was found[1,4] to have the desired pharmacologic actions and to be compatible with isopropyl arterenol. Tablets containing 10 mgm isopropyl arterenol and 100 mgm benzyl nicotinamide* were prepared for sublingual use and were evaluated clinically.

The series of patients for this study includes fifty asthmatics, of whom thirty were men and twenty were women. The average age was forty years, with extremes being five years and seventy-six years. Forty of these patients were classified as chronic asthmatics, and ten patients as acute since they had not received any previous therapy for asthma. The diagnosis was definitely established in each case by a careful history survey, physical examination and required laboratory studies.

All of the chronic cases in this study had been treated with isopropyl arterenol alone, but the drug was discontinued because of equivocal therapeutic results. These patients were given one tablet of benzyl nicotinamide with isopropyl arterenol sublingually three times daily. The shortest interval between any two doses was two hours.

The acute cases were alternated, with epinephrine being given parenterally to the odd numbered cases and benzyl nicotinamide with isopropyl arterenol being given sublingually to the even numbered cases. It was observed that the experimental group was as adequately controlled as the epinephrine control group.

The clinical results obtained in both acute and chronic asthmatic cases were more than gratifying. In forty-three patients very good to excellent results were obtained, in five patients the results were fair to good and in two patients the symptoms were not relieved at all. There were relatively few side effects and, when they did occur, they were mild. A few patients occasionally complained of a bitter taste, but this complaint was not severe enough to interrupt therapy. Several patients swallowed the tablets and complained of mild gastrointestinal disturbances. When they were impressed with the necessity of taking the tablets as directed, by the subligual route, there were no further complaints.

SUMMARY

1. A new antispasmodic preparation containing benzyl nicotinamide, 100 mgm, and isopropyl arterenol, 10 mgm, in a sublingual tablet was evaluated in fifty patients.

2. Forty of these patients were chronic asthmatic cases and had previously been treated with isopropyl arterenol alone without too much success.

3. Ten patients were classified as acute asthmatic cases.

4. In forty-three of the fifty cases, the results with benzyl nicotinamide plus isopropyl arterenol were very good to excellent.

*Supplied by the Medical Research Department, The National Drug Company, Philadelphia 44, Pennsylvania.

5. In five cases the results were fair to good.
6. In two cases the symptoms were not relieved at all.

CONCLUSION

Asthma therapy with the combination of benzyl nicotinamide-isopropyl arterenol was found to be similar to that with isopropyl arterenol alone, but more effective. The combination seemed to be more rapidly absorbed and to produce relatively fewer and milder side effects. Clinically, this easily administered sublingual preparation was found to be an excellent symptomatic remedy for rapid temporary relief of bronchial asthma.

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1930 Chestnut Street

SOUTHEASTERN ALLERGY ASSOCIATION

At a recent meeting of the Southwestern Allergy Association, the following officers were elected:

President: Lindsay Miller, M.D., Gadsden, Alabama

President-Elect: Walker L. Rucks, M.D., Memphis, Tennessee

First Vice President: James Overall, M.D., Nashville, Tennessee

Second Vice President: John Guerrant, M.D., Charlottesville, Virginia

Secretary-Treasurer: Katharine B. MacInnis, M.D., Columbia, South Carolina

Committeemen-At-Large: Andrew Taylor, M.D., Charlotte, North Carolina

Thomas Collier, M.D., Brunswick, Georgia

SURVEY OF AIRBORNE POLLEN AND FUNGUS SPORES IN ISRAEL, 1951-1952

ARTHUR KESSLER, M.D.
Tel-Aviv, Israel

THIS is a survey of atmospheric incidence of pollen and macroconidia of fungi in the center of the town Tel-Aviv—Jaffa (coast plain of Israel) during the years 1951 and 1952.

POLLEN SURVEY, 1951

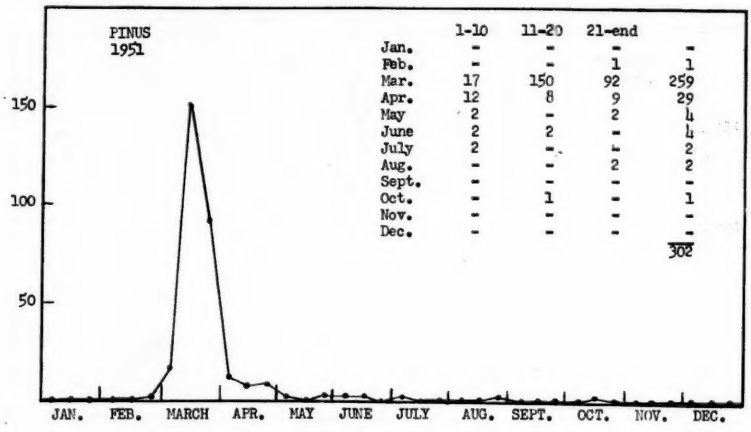
The following numbers and graphs give a survey of the atmospheric incidence of pollen in the center of Tel-Aviv—Jaffa throughout the year 1951. They are made with the slide method and count over a whole square of 18 mm side length (3.24 cm^2 slide area, which is covered with a cover glass of 18 mm side length). The counts are made daily; in the post-seasonal period exposure is lengthened to two to three days. The numbers in the graphs are the total result of a ten days' period.

Figure 1 gives the incidence of pine pollens. Pine pollens are easily identified because of their air bladders. In the town there are many public gardens and house gardens with numerous pine trees. The nearest forest of pine trees is found in the mountain regions about 25 km from the town. Pollination begins in the middle of February, the highest incidence is in the middle of March. By the beginning of April the massive infection of the atmosphere is finished, but the incidence of late blooming carries through until July. Completely isolated pollens were found at the end of August and the middle of October. The year 1951 was a dry year, with short and heavy blooming. The form of the graph for 1952 (Fig. 4) is completely different, although the beginning and the end are identical. No clinical importance is attributed to pines. Even for patients in the Haifa region, where the pines of the Carmel Mountain are very dense, and where many patients themselves attribute their symptoms to pines, it was found through tests and exposure that there was another cause, mostly grasses or in many cases *Olea europea* pollens.

Other tree pollens which were seen on the slides many times are: Acacia pollen (March), easily identifiable by their characteristic shape; Eucalyptus pollen (January through May); Olive pollen (throughout March and April), identifiable by their color and regular granulation. Their incidence is fairly high. Their allergenic character seems to me to be proved through tests, exposure and therapy and will be the theme of a later communication. Citrus pollens (April) are often found on the slides at the same time as the pollen of grasses. They are differentiated through their more rectangular form as against the oval form of the olea pollen. Since the land is

From the Allergy Clinic of the Workers Sick-Fund.

overrun with citrus groves, it is not unusual that a large number of patients suffering from typical hay fever from grass pollen attribute their allergy to the widely prevalent citrus blooms with their heavy odor. Not a single



	1-10	11-20	21-end	
Jan.	-	-	-	-
Feb.	-	-	1	1
Mar.	17	150	92	259
Apr.	12	8	9	29
May	2	-	2	4
June	2	2	-	4
July	2	-	-	2
Aug.	-	-	2	2
Sept.	-	-	-	-
Oct.	-	1	-	1
Nov.	-	-	-	-
Dec.	-	-	-	-
				302

Fig. 1. Incidence of Pine Pollens in the center of Tel-Aviv—Jaffa, 1951.

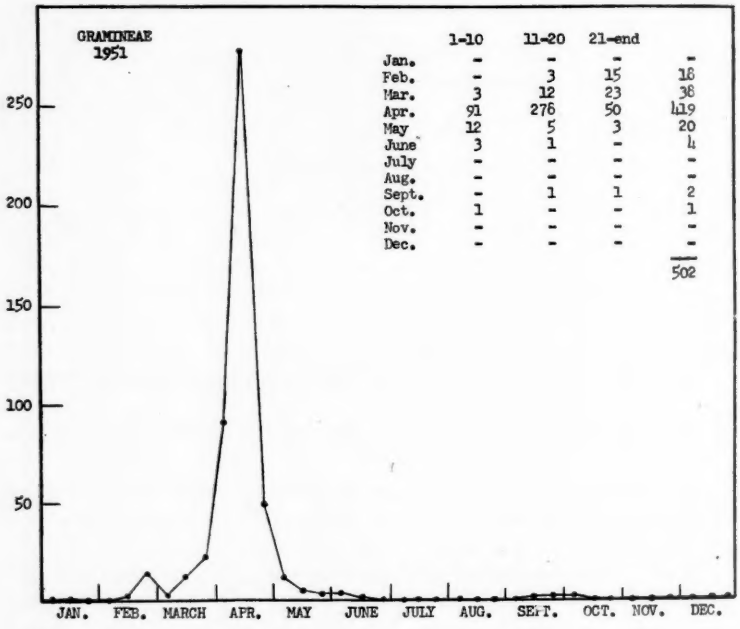
case of rhinitis, conjuctivitis or asthma which appeared for investigation could be proved sensitive to citrus pollen. Nearly all were hay fever patients sensitive to grasses.

Figure 2 shows the pollen incidence of grasses throughout the year 1951 in the center of Tel-Aviv—Jaffa. In February there was a low degree of pollination. The very beginning of the increase is in the middle of March, reaching a peak in the middle of April, where the incidence in the daily survey jumps to 8.58 pro cm² ($\frac{278}{10}$: 3.24). In the second half of May and in June the numbers are low. The year 1951, as previously mentioned, was very dry with little rain in the preceding rainy period 1950/51. A comparison of this period with the same period in 1952 (Fig. 5) nevertheless shows only a small difference. An autumnal season as described by Gutmann[1] was not found on the slides in the dry year 1951.

Single grass pollens are also noted outside the pollen season. Bermuda Grass (*Cynodon dactylon*), which is densely spread over lawns and also grows wild, has no special time of flourishing; but in humid places, such as near stables, dripping taps, channels, or in gardens with irrigated lawns, is to be found in flourishing patches at any time of the year. Although the extraseasonal incidence of grass pollens is insufficient to pollute the atmosphere or be prevalent on the slides, they are in sufficient quantity to produce incidentally attacks of pollinosis. Their perennial presence may produce perennial respiratory symptoms which may include bronchial

asthma as well as hay fever. This group requires special attention and will be the subject of a special investigation.

Pollens of the Compositae family, with their spiny surfaces, are frequent-



	1-10	11-20	21-end	
Jan.	-	-	-	-
Feb.	-	3	15	18
Mar.	3	12	23	38
Apr.	91	276	50	419
May	12	5	3	20
June	3	1	-	4
July	-	-	-	-
Aug.	-	-	-	-
Sept.	-	1	1	2
Oct.	1	-	-	1
Nov.	-	-	-	-
Dec.	-	-	-	-
				502

Fig. 2. Incidence of Grass Pollens in the center of Tel-Aviv—Jaffa, 1951.

ly noted on the slides singly or in groups. A clinical ragweed season is practically nonexistent. From May to November there is no rainfall. In July, August, and September there are to be found pollens of the Amaranthus family in relatively large numbers. Many other pollens, which are partly identifiable because of their special shapes and by comparison with field investigations or which can be recognized only by experienced botanists, are to be found on the slides. It should be mentioned that throughout the whole year pollens are always to be found on the slides because no cover of snow ever remains on the ground.

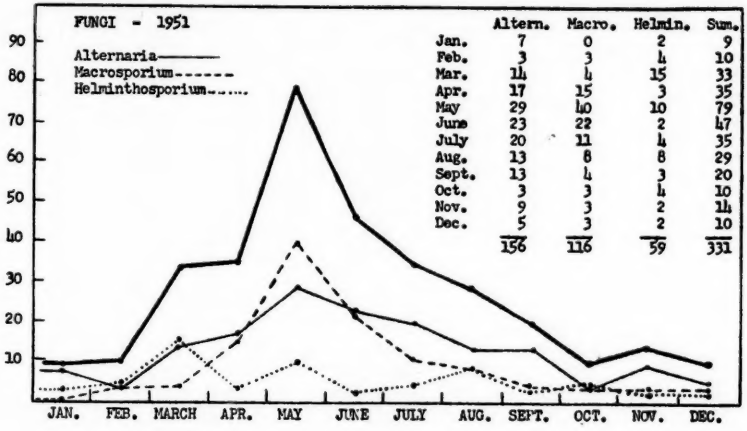
This is a survey of the atmospheric pollen incidence in Israel in the dry year 1951.

SURVEY OF AIRBORNE FUNGUS SPORES, 1951

This is a survey of certain spores of molds during the year 1951 in the center of Tel-Aviv—Jaffa.

The macroconidia of *Alternaria, Macrosporium, Helminthosporium* were

counted and observations were made of the incidence of *Cladosporium-Hormodendrum, Fusarium.* The macroconidia of these fungi are easily recognized on the slides, they are of the highest incidence in the atmos-



	Altern.	Macro.	Helmin.	Sum.
Jan.	7	0	2	9
Feb.	3	3	4	10
Mar.	14	4	15	33
Apr.	17	15	3	35
May	29	40	10	79
June	23	22	2	47
July	20	11	4	35
Aug.	13	8	8	29
Sept.	13	4	3	20
Oct.	3	3	4	10
Nov.	9	3	2	14
Dec.	5	3	2	10
	156	116	59	331

Fig. 3. Atmospheric incidence of macroconidia of fungi in Israel, 1951.

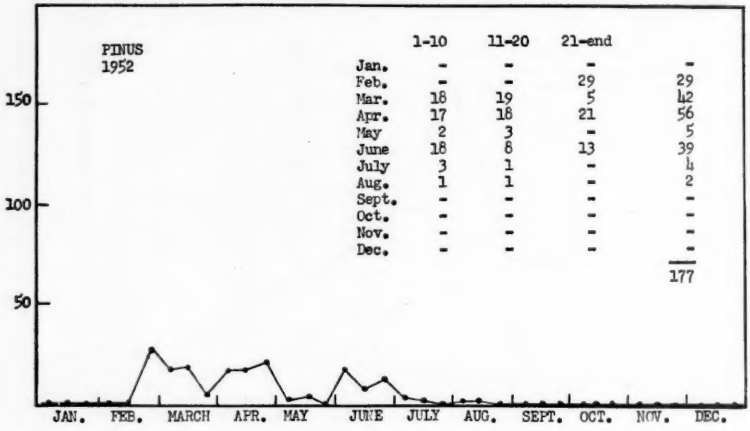
phere and are also of a high group incidence in a group of 2,000 patients who are being tested intracutaneously and cutaneously with various fungi allergens. The same fungi have been widely found in the dark patches on the walls, so familiar in the humid winter months, as well as on vegetables and other food.

The figures represent the counting over a whole square of 18 mm side length of the petrol-covered slide and are added in monthly periods. The graph (Fig. 3) shows a maximum of atmospheric total incidence of Dematiaceae in May. It is remarkable that the maximum of Gramineae pollen incidence falls in the same area in the middle of April, and there are cases of common sensitivity to pollens and molds whose symptoms are probably protracted by this fact. The rain period in winter 1951/1952 was below the medium. The report for 1952, after a winter of much rain, will clear up this proportion. The curves for *Alternaria* and *Macrosporium* are in the essential details equal to the total curve with the peak in May. Also the total yearly figures of these two groups are not considerably different. (Yearly figure of *Alternaria* is 156, of *Macrosporium,* 116). Helminthosporium is equally spread over the year without seasonal movements and the total annual figure is smaller (59). Cladosporium-Hormodendrum were often seen on the slides as single or double spores, or in groups. Fusarium was rarely seen.

This is a survey of slide observations of the atmospheric incidence of macroconidia of fungi in Israel in the year 1951.

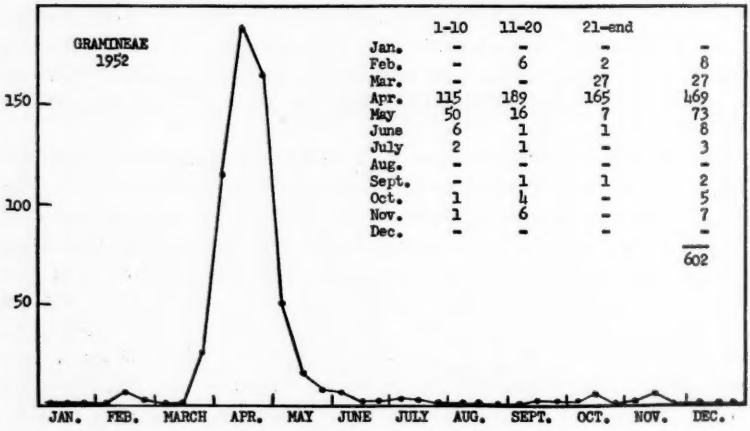
SURVEY OF AIRBORNE POLLEN AND MOLDS, 1952

This is a survey of airborne pollen and molds throughout the year 1952 in the center of Tel-Aviv—Jaffa.



	1-10	11-20	21-end	
Jan.	-	-	-	-
Feb.	-	-	29	29
Mar.	18	19	5	42
Apr.	17	18	21	56
May	2	3	-	5
June	18	8	13	39
July	3	1	-	4
Aug.	1	1	-	2
Sept.	-	-	-	-
Oct.	-	-	-	-
Nov.	-	-	-	-
Dec.	-	-	-	-
				177

Fig. 4. Incidence of Pine Pollens in the center of Tel-Aviv—Jaffa, 1952.



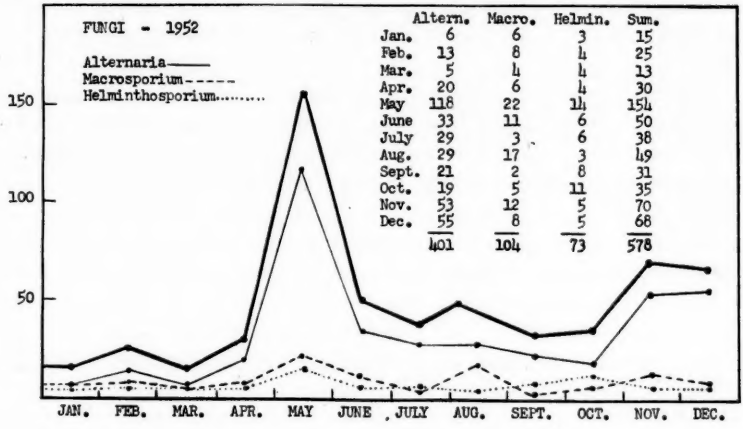
	1-10	11-20	21-end	
Jan.	-	-	-	-
Feb.	-	6	2	8
Mar.	-	-	27	27
Apr.	115	189	165	469
May	50	16	7	73
June	6	1	1	8
July	2	1	-	3
Aug.	-	-	-	-
Sept.	-	1	1	2
Oct.	1	4	-	5
Nov.	1	6	-	7
Dec.	-	-	-	-
				602

Fig. 5. Incidence of Grass Pollens in the center of Tel-Aviv—Jaffa, 1952.

After a winter of substantial rainfall, the picture in the year 1952 varied in some respects from that of the previous year. The pollination of *Pinus* (Fig. 4) started during a period of rainy days at the end of February. The curve is lower and wider spread. The numbers vary equally, about twenty for every ten days' period. There are no peak numbers. Blossom time finished only at the end of June and small numbers were

found until the middle of August. The general number of pollen is 177, which is considerably less than that of 1951 (302).

The curve for grass pollen (Fig. 5) is lower and broader than in 1951,



	Altern.	Macro.	Helmin.	Sum.
Jan.	6	6	3	15
Feb.	13	8	4	25
Mar.	5	4	4	13
Apr.	20	6	4	30
May	118	22	14	154
June	33	11	6	50
July	29	3	6	38
Aug.	29	17	3	49
Sept.	21	2	8	31
Oct.	19	5	11	35
Nov.	53	12	5	70
Dec.	55	8	5	68
	401	104	73	578

Fig. 6. Atmospheric incidence of macroconidia of fungi in Israel, 1952.

with equal start and finish and again reaching peak point by the middle of April. The total number is higher than in 1951 (602 against 502). The autumnal season, which was almost not marked on the slides in September and October, 1951, was more distinct in 1952 during the months of September, October and November. The number of hay fever patients with season symptoms in the spring pollination time, who also showed an autumnal season, was considerable in 1952.

Composite pollen, with thorny surfaces, was found through nearly all the months (January, March, April, May, June, July, October), often in groups of ten to fifteen.

From the middle of August, *Amaranthus* pollen was richly found on the slides. Arranged in ten-day periods, the numbers are:

August	0	3	5
September	13	5	18
October	23	16	24
November	2	2	5
December	11	0	0

(All figures refer to an area of the slide covered by a cover glass of 18 mm side length.) At this time, in the middle of December, a series of days of high temperature and low humidity ("Khamsin") with subsequent rains brought the pollination to an end.

The mold curves (Fig. 6—note that the scale was being changed) of

1952 are similar in their form to those of the previous year. May is the month with the highest number of Macrospores found on the slides. *Alternaria* spores are the most frequent macronidia. The total number of *Alternaria* is more than double that of 1951 (401 against 156). For *Macrosporium* and *Helminthosporium,* the form of the curves, the total numbers and the proportion of the numbers to each other are quite unchanged.

Skins of insects were often found, in certain months in greater numbers, especially in April, May, June, October and November, likewise scales from insect wings. Of the locusts which flew over the town on April 26, and in smaller swarms on June 18, no certain traces were found on the slides.

This is a survey of slide observations of the atmospheric incidence of pollen, macroconidia of fungi, insect residues in Israel in the year 1952.

REFERENCE

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11 Weisel Street

ISOTOPES AID IN DIAGNOSIS AND TREATMENT

Articles by thirty leaders in the atomic energy field appear in a transcript released by the National Industrial Conference Board. The following recognized authorities on medical and pharmaceutical applications of atomic energy are among those represented:

Donalee L. Tabern, Head, Department of Radioactive Pharmaceuticals, Abbott Laboratories.

Bernard Roswit, M.D., Director, Radioisotope Unit, U. S. Veterans Administration Hospital, Bronx.

Edith H. Quimby, M.D., Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University.

D. A. McGinty, Laboratory Director in Physiological Research, Parke, Davis & Company.

Charles Rosenblum, Head, Radioactivity Laboratory, Merck & Co., Inc.

Subjects covered include medical and pharmaceutical applications of atomic energy, agricultural and food processing applications, current uses of atomic by-products in industry, the place of nuclear power in the nation's power supply and problems of industrial participation in atomic power development.

This publication brings together for the first time the combined thinking of leaders in the applications of atomic energy and its by-products in the medical, pharmaceutical, agricultural and industrial fields.

Costs Less Than Radium.—The unit has produced more radioactivity in the form of Gold-198 alone, than all of the radium in all the hospitals in the United States put together. Economically, the important fact is that this activity has been produced, handled, and distributed at a cost infinitely less than the cost of a comparable amount of radium.

Selecting but one use alone, it would be conservative to say that somewhere between 50 and 65 per cent of the patients suffering from ascitic fluid accumulation

(Continued on Page 335)

HEADACHE AND TENSION

Cause or Effect

HENRY D. OGDEN, M.D., F.A.C.A.
New Orleans, Louisiana

OUR headache studies have been reported.[1,2,3,4,5,6] In the cross section survey of 4,634 individuals, we found an incidence of headache of 64.8 per cent in the groups studied. This incidence was shown to vary in different types of individuals.[3]

It was found that migraine is but one variety of a much larger (and at present possibly nondescript) galaxy of vascular headaches.[5] The incidence of some headache patterns depends on the definition of the investigator. As an example, we found that histamine cephalalgia (when rigidly defined) was a clinical rarity.[5] Another worker with a broader concept of histamine cephalalgia will report a much greater incidence. Therefore, the definition and boundaries of the vascular headaches are of paramount importance. We found that the frontal type of headache far exceeded other varieties. There is also the fairly generalized diffuse headache, the occipital type, and probably others.

Factors of tension, occupation, emotion, et cetera, were seen to be of great importance and significance.[3,6] It is therefore important never to lose sight of the significance of psychogenic factors. However, just as dangerous an oversight would be to relegate other factors such as allergy, for example, to a minor, irrelevant, or nonexisting role. The background of headache has several component parts. It is incomplete when perspective is distorted by overemphasizing the importance of any one of its parts.

It is felt therefore that the headache background may vary in different people, with emphasis in some on certain of the factors and in others, of other factors. The background is necessarily complex, and careful studies of an individual from various aspects are ideal. The interrelationship of these factors can only be appreciated by one who has an "overall" viewpoint. Also, as pointed out by Unger and Unger,[7] a specified factor such as stress, may on occasion cause symptoms. In the same individual on another occasion the stress factor may be relatively small but an increased allergic factor could precipitate symptoms. This same concept may be broadened to include other contributing disturbances.

It is also thought that oversimplification of the problem can extend to attempts at determining the specific mechanism. In reality more than one mechanism may exist in the same individual at the same time and at different times.

Let us discuss the personality changes that are generally accepted as being characteristic of migraine or in fact of many other headaches. It

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is my observation that headache patients may be difficult to handle; at times unpleasant, and possibly uncoöperative, demanding and aggressive. They are often impatient and intolerant of anything except immediate results. This personality pattern is generally tied in with the migrainous individual as a cause of his condition. Therefore, the thought is herewith advanced that the personality changes may at times be secondary to the headache state—rather than a cause. The patient who obtains relief may become more pleasant and less "tense."

The physician who is interested in headache often sees many individuals who have just about exhausted the possibilities of aid that may be given to them by various medical specialties.

Another point to consider is the fact that at times the headache patient may obtain dramatic relief from some spectacular procedure. As an example, refraction and the wearing of glasses may relieve headache for a period of time, possibly weeks or months. Then the headaches return in their former intensity. There are several medical procedures which may be regarded by the layman as being spectacular or dramatic. An allergy survey, a psychiatric study, psychoanalysis, teeth extraction, gynecologic surgery, sinus operation, other nasal surgery, et cetera, may fall into this category.

The real truth is, as above stated, the headache background has several factors. All of these factors must be properly managed in order to obtain adequate benefit.

Let us next consider some of the problems and questions that call for further study.

First, the vascular headaches should be more clearly defined. Other possible mechanisms must not be disregarded. As an example, we feel that frontal headache is essentially due to a reflex mechanism in which dilation of certain vessels results from nasal mucosal edema.

Another problem revolves around the better use of symptomatic agents which are currently available. As an example, careful study in the future may reveal that there is a place for a well-timed vasodilator in the stage of vasoconstriction even though past results obtained with such preparations have been variable.

The ergotamine drugs have proved themselves. There may be other and more advantageous methods in which to use them. Another thought is the necessity of accommodating mixed factors. Thus, where a vascular factor coexists with a myalgic factor, a vasconstrictor alone might well do its job and still leave the patient in intense pain from an untreated myalgia, and vice versa. The concomitant use of an effective vasoconstrictor with an analgesic combination should never be overlooked in cases refractive to a single approach. If the stress factor is also high, there may be need for suitable sedation. If the allergic factor is high, there may be need for suitable allergic management as well, including hyposensitization, antihistamines, and so on.

DISCUSSION

We feel that tension is a factor in all headaches, and that the classification of a headache type as being "tension headache" is too all-embracing to be definitive. When the vascular headaches are better understood, this classification may disappear. Using the same reasoning a myalgic headache may be almost totally a scalp muscle pain, or it may be simply the end result of a severe vascular headache. In the latter case it would be an effect. If tension does not cause a given headache, it certainly will be precipitated by the headache state. This is the reason for the administration of such drugs as Fiorinal, which combine analgesic and sedative action with limited vasoconstrictor effect.

CONCLUSIONS

1. Personality changes associated with headache may be the result of the headache state, and not necessarily the cause.

2. A dramatic medical procedure may relieve vascular headache for a varying period of time, without removing the true cause.

ACKNOWLEDGMENT

Acknowledgment is made of the assistance of Mr. James Villere, Southwest Manager of Sandoz Pharmaceuticals.

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ANTIGENS FROM ADULT AND LARVAL FORMS OF TRICHINELLA SPIRALIS

Test antigens prepared respectively from adult and from larval forms of trichina were compared by means of the complement fixation test on serum from rabbits infected experimentally with varying numbers of trichinae. It had been hoped that by using an "adult" test antigen significant serum reactivity could be detected earlier during the course of infection than with the usual "larval" antigen. Although significant levels of reactivity were shown to occur with "adult" antigen, this form of antigen had no apparent advantage over the larval form of antigen in the detection of antibodies during early stages of trichinosis.—*Canadian Journal of Medical Sciences.* Abstract. J.A.M.A., 151:1141 (June) 1953.

SCHONLEIN-HENOCH SYNDROME
With Report of a Case

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THE CASE of Schonlein-Henoch Syndrome here presented is an example of the disease entity discussed later.

CASE REPORT

The patient, E. T., is a three-year-old white female child. She was first seen on December 4, 1951, with bilateral otitis media and at that time she was given 300,000 units of penicillin. The otitis media improved on the next day, but flared up again on December 6, 1951, at which time she had another 300,000 units of penicillin. On December 7, 1951, she developed nausea and vomiting with abdominal pain. The otitis media was definitely improved at this time. On December 8, 1951, the abdominal pain and the nausea and vomiting became progressively worse. She also developed blood in her stools. Her temperature was 100 degrees. She was put on parenteral fluids and gradually improved, but on December 13, 1951, the abdominal pains became more severe and were constant in duration. The abdominal pains were generalized and crampy in character. The abdomen was also tender throughout and some muscle rigidity was present. She could not retain any food, including water. On December 16, 1951, she was hospitalized because the diagnosis of an intussusception was considered. On admission to the hospital her blood counts were normal. On the day following admission to the hospital the patient developed tarry stools, joint pains, ecchymotic spots in the joint areas and a few on the posterior aspect of her legs and buttocks. At this time I considered the diagnosis of Schonlein-Henoch Syndrome. Her blood studies were normal except that she had developed a secondary anemia from the intestinal bleeding. She was given a blood transfusion, glucose and lactate-ringers solutions intravenously. The child was also put on parenteral vitamin C, K, and B-complex. I decided it might be of some help to also give her histadyl parenterally.

On the fourth hospital day the patient was able to take some clear liquids by mouth, but it was not until the tenth hospital day that she was able to tolerate a soft diet. She continued to have blood in her stools until two days before discharge from the hospital. She gradually improved and was discharged on December 30, 1951. From this time until March 1, 1952, she had recurrent episodes of vomiting, abdominal pains, joint pains, and an exanthema which started with hives and in twenty-four hours would change to red purpuric spots and then gradually fade away in a few days. The purpuric rash would appear on the buttocks and posterior aspect of her legs and some on the flexor surfaces of the elbows. When the urticaria appeared, it seemed to be more general in distribution, including the scalp. At first these symptoms would recur every ten days, but by the first of February the symptoms recurred every two to three days.

The child was hospitalized on March 1, 1952, and put on a strict elimination diet since food allergy was suspected as a causative factor at this time. Within forty-eight hours she appeared markedly improved. She was discharged on March 3, 1952, and maintained on the same diet. Egg was the only food which gave her a few symptoms. The ingestion of egg produced ecchymotic spots on her legs and the child complained of fatigue and some generalized abdominal pain. Since March, 1952, the patient has had no recurrence of symptoms. She has gained weight, sleeps well, and has an apparently improved disposition.

It is well to note that on July 9, 1949, this patient had penicillin for an otitis media. On January 2, 1950, she again had otitis media and again received penicillin. The day following this injection of penicillin she developed vomiting and abdominal cramps. She was put on parenteral fluids and her symptoms cleared up in three or four days. Undoubtedly, the penicillin was the main allergen causing the allergic response in this child. The previous history of penicillin injection and subsequent reactions would substantiate this.

The Schonlein-Henoch Syndrome is an allergic entity. It is sometimes referred to as "Anaphylactoid Purpura," "Allergic Purpura," and "Schonlein's Disease" or "Henoch's Purpura" depending on the characteristic clinical manifestations of the disease. The syndrome is characterized by three main symptoms: first, an exanthem; secondly, gastro-intestinal symptoms, such as, colic, vomiting, and hemorrhage from the intestine; and lastly, painful swellings of the joints. Hematuria may or may not be present. Recurrences of one or more of these symptoms are characteristic of the disease.

Robert Willan in 1808 gave the first description of this syndrome. However, the condition was not recognized as an entity until Johann Schonlein in 1837 described the combination of joint symptoms with a rash peliosis (livid) rheumatica. Apparently, very little attention was paid to this entity until Edouard Henoch in 1868 reported the first case with symptoms of colic, bloody diarrhea, painful joints, and a rash. Henoch emphasized the frequent association of nephritis in his later cases. Osler described a number of these cases and was the first to suggest, in 1914, the possible relationship of allergy to this condition. But it was not until 1927, when H. L. Alexander and C. H. Eyermann showed the relationship of the syndrome to allergy. Their first cases were due to food allergies and they were able to reproduce the symptoms by ingestion of the offending food.

This condition is rather rare. I believe, however, more cases exist, but are not recognized as an entity. Apparently it occurs more often in males and usually falls in the age group of three to fifteen years of age. It may occur in adults, but has rarely, if ever, been described under two years of age. The disease is due to a hypersensitivity reaction where the antigen may be either bacterial or non-bacterial in origin. Foods, drugs, and infection have been named as common causative factors.

The various manifestations of the disease are the result of a vascular lesion. The joint symptoms resemble serum disease. The classic capillary lesions are represented by active inflammatory changes centered around the smallest vessels with infiltration of inflammatory cells, and destruction and dilatation of capillaries. Edema of the epidermis and corium may also be present in the affected areas. In the neighborhood of the larger infiltrations the collagen is swollen, but fibrinoid degeneration of collagen is not present. The swelling of the joints is due to periarticular edema rather than to effusion into the joint.

The characteristic gastrointestinal symptoms are colic, blood in the stools, and vomiting. The terminal ileum is the segment usually affected, although the whole small intestine, cecum, and ascending colon have been involved. The joint symptoms consist of transient puffiness of a single joint to recurrent painful swelling of many joints. Fever is low grade, if present. The exanthem may start with urticarial lesions. Within a few hours to a day they begin to change to pink maculo-papules, becoming progressively less raised and darker in color. In a day or two the lesions become dark red macules which do not fade on pressure. From this stage there is slow regression, the red color becoming more purple before fading to brown and finally disappearing altogether by the end of one or two weeks. Most frequently affected sites are the buttocks and lower back, around backs of elbows and extensor surfaces of the arms, and on the extensor surfaces of the lower leg. The lesions are usually symmetrical. At times frankly hemorrhagic lesions are seen varying from small petechiae to ecchymoses.

Usually the diagnosis can be made by the presence of the characteristic symptoms. The disease can be readily differentiated from other purpuras because of normal prothrombin time, bleeding time, clot retraction time, blood platelets, and coagulation time. Capillary resistance is normal. The gastrointestinal symptoms may simulate appendicitis and intussusception. Clinically, it is impossible to differentiate hemorrhage into the bowel wall and intussusception complicating purpura because both cause signs and symptoms of intestinal obstruction and both may be associated with a palpable mass. Laparotomy is therefore indicated early. Several deaths have been reported of Anaphylactoid Purpura complicated by intussusception without operative intervention.

The prognosis is generally good. Death can occur from this disease. If the condition is complicated with nephritis, the prognosis is grave.

There is no known treatment for this syndrome. If the offending allergen can be found, its elimination usually can result in the disappearance of the symptoms. Drug sensitivities, especially the antibiotics, have to be guarded against. Ascorbic acid, vitamin K, rutin, and antihistamines have been tried, but none are specific. However, I believe that ascorbic acid and antihistamines should be used in the treatment of this purpura. ACTH and cortisone may be of value in the severe cases..

SUMMARY

A case of Schonlein-Henoch Syndrome is described. Penicillin was suspected as the chief causative factor and egg sensitivity probably played a secondary role. The syndrome is summarized. It may be well to stress that more of these cases exist than are diagnosed.

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ISOTOPES AID IN DIAGNOSIS AND TREATMENT

(Continued from Page 328)

in association with ovarian tumors have been given symptomatic relief for anywhere from a few weeks to over several years.

Patients (27 of 50) with Prostate Tumors Helped.—The University of Iowa group presented before the American Roentgen Ray Society meeting in Houston, their reports upon the treatment of fifty consecutive prostate tumors. Practically all of these have failed to respond to other types of treatment. Today, twenty-seven of these fifty are alive with no obvious clinical evidence of disease, and ten of them have been shown on biopsy to have no tumor tissue. What the story will be later on, only time will tell, but certainly most intriguing channels of investigational treatment have been opened up by means of this one radioisotope alone.

Clinical Experience Urgently Needed.—The training of radioisotope personnel has been in many respects a throw-back to the apprentice technique. An individual or a group of individuals have become interested. They have taken certain basic courses, in physics, nuclear physics, and chemistry. They have in all probability taken one of the courses given by the Oak Ridge Institute of Nuclear Studies. However, none of this has given them the clinical experience that they actually need. To do this they must work day in and day out for suitable periods as a part of groups carefully and intelligently making use of radioisotopes. From there they go on to their own institutions or to the establishment of new radioisotpe centers. We believe that more and more of this should be centered about places like the Oak Ridge Institute Hospital and we hope that the opportunity to see and perhaps even ultimately participate in the handling of radioisotopes in an institution such as that in Oak Ridge will contribute materially to the better handling and use of radioisotopes.

Five radioisotopes have been found to be successful in the treatment of human diseases:

Radioisotope	Therapeutic Use
1. Radioiodine I^{131}	Toxic-hyperthyroidism Cancer of the thyroid gland Advanced heart disease and angina pectoris
2. Radiophosphorus P^{32}	Polycythemia vera Chronic leukemia Diseases of the skin, benign and malignant
3. Radiogold Au^{198} (colloidal form)	Advanced cancer with excessive fluid in chest or abdomen Cancer of the prostate gland
4. Radiostrontium Sr^{90}	Diseases of the eye, benign and malignant
5. Radiocobalt Co^{60}	Deep-seated internal cancer

Typical Medical Uses of Isotopes.—At present the most widely employed diagnostic test with a radiosotope is the use of I^{131} in determining thyroid function.

Transcripts of this symposium, the most comprehensive conducted to date on medical, pharmaceutical, agricultural and industrial applications of atomic energy, are available upon request, from the National Industrial Conference Board, 247 Park Avenue, New York 17, New York.

ADJUNCT TREATMENT OF CERTAIN ALLERGIES RESPONDING UNSATISFACTORILY TO CONVENTIONAL THERAPY

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THE MAJORITY of the 16,000,000 persons in the United States who suffer from one or more major allergies responds favorably to conventional means of allergic management, but a substantial minority fails to get satisfactory relief by these procedures alone. This latter group requires adjunct therapy for adequate control of clinical symptoms.

Reports of dramatic results achieved by treating allergic conditions with ACTH and cortisone fill the literature. Used as nonspecific therapeutic agents, these hormones initiate early relief of allergic symptoms in a wide variety of conditions including bronchial asthma, [1,2,4,5,7,12,18,19,23,28] status asthmaticus,[11,19] hay fever,[21,31] allergic rhinitis,[14,30] eczema,[3,10] drug reactions,[6] atopic dermatitis,[15,27,35] neurodermatitis,[10] urticaria and serum sickness.[33]

However, the literature also contains extensive reports on toxic reactions involving practically every domain of the body resulting from the indiscriminate use of these hormones. Symptoms generally recur shortly after discontinuation of ACTH or cortisone, and the exacerbation is frequently more severe than the original condition. On the other hand, if hormone therapy is continued to the extent required to control allergic conditions, there is the constant danger of deleterious side effects involving glands of internal secretion, gonadal function, electrolyte balance, cardiovascular system, muscular activity, the central nervous system, mental processes, and the gastrointestinal tract.[8,39]

These indications make it evident that ACTH and cortisone may be used to good effect in bringing acute allergic symptoms under control, but that continued use of the hormones, or withdrawal of them without instituting other adequate means of control, may lead to serious side effects or severe exacerbation.

In the search for a means to achieve satisfactory management of allergic cases which could not be adequately controlled by conventional measures, and at the same time avoid as far as possible the potential problems associated with ACTH and cortisone therapy, our attention was called by Randolph[29] and others to a nonspecific agent which produces a blood response in allergic individuals somewhat similar to that instituted by administration of ACTH. This drug is Piromen,* a *Pseudomonas* polysaccharide prepared in colloidal dispersion for parenteral use. It is sterile, nonprotein, nontoxic and nonanaphylactogenic.[25]

*Piromen (formerly known as Pyromen), is a product of Travenol Laboratories, Inc., a subsidiary of Baxter Laboratories, Inc., Morton Grove, Illinois.

One of the most characteristic features of allergic disease is blood eosinophilia. Hansel[17] has stated that where there is allergy there must be eosinophils. While the function or part this cell plays in the allergic reaction is not known, it is generally accepted that relief from allergic symptoms is associated with a reduction in eosinophils.

When ACTH or cortisone is administered to an allergic individual with eosinophilia there is a sharp eosinopenia which may last as long as four or five days. In the response the eosinophil count falls almost to zero, as shown in Figure 1.

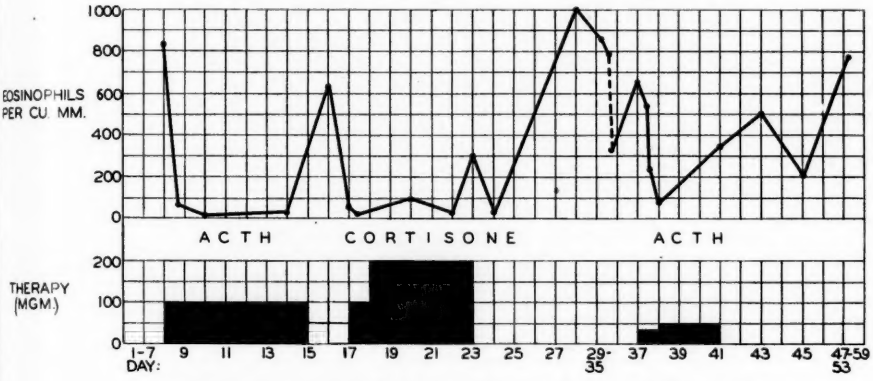

Fig. 1. The influence of ACTH and cortisone upon eosinophils is shown by the above chart of L. S., a patient with an exfoliative dermatitis probably due to a lymphoblastoma, who developed a multiform erythematous eruption and serum sickness-like reaction during ACTH therapy. (Reprinted from the Proceedings of the Second Clinical ACTH Conference, Vol. 2, p. 397, courtesy Dr. Gordon C. Sauer.)

When Piromen is given under similar conditions it also suppresses the eosinophils, although the eosinopenia is not so marked or prolonged as that following ACTH. Randolph and Rollins[29] have demonstrated that immediately after a two gamma (microgram) intravenous injection of Piromen in the allergic individual there is a transient leukopenia followed by a pronounced leukocytosis, lymphopenia and eosinopenia. A classic example is shown in Figure 2. The eosinophil pattern of the same allergic person when Piromen was given over a period of several days is shown in Figure 3. In the latter response there is gradual but steady suppression of the eosinophil level day by day. This blood response resembles an adrenocorticotropic-like action and there is no evidence in the literature that it is the result of a toxic reaction.

The leukocytosis produced by administration of Piromen offers added protection against secondary infection, often encountered in allergic management. This is in contrast to the use of ACTH or cortisone which tend to modify the reaction of the body to microbial invasion. Use of the hormones also may impair diagnosis and evaluation of infections.[8]

The action of Piromen is not entirely understood. It has been determined that the drug stimulates the reticulo-endothelial system,[22,26] and Windle[38] and his associates have demonstrated stimulation of the reticular zone of the adrenal cortex. However, Soylemezoglu and Wells[34] have found that adrenalectomized dogs show a typical blood response to

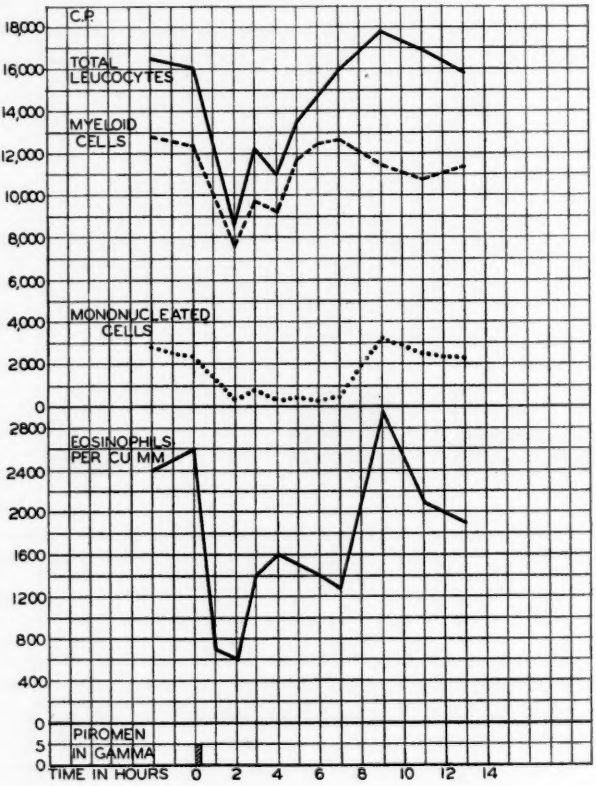

Fig. 2. This is a characteristic blood response following a single intravenous injection of Piromen in C. P., a patient with a diagnosis of severe bronchial asthma and allergic rhinitis with nasal polypi. (Reprinted from Annals of Allergy, 8:626-640 (Sept.-Oct.) 1950, courtesy of Dr. Theron G. Randolph.)

Piromen and conclude that Piromen produces its change in leukocyte counts by mechanisms other than pituitary-adrenal discharge. It has been shown by Code[9] and subsequently others[13] that ACTH and cortisone do not influence immunologic response and do not participate in antibody formation, and Samter[32] has reported similar findings in guinea pigs after Piromen administration.

Piromen is a safe therapeutic agent.[16,20,24,29,40,41] The report in the literature on a death[36] following its use seems to be a coincidental occurrence.

The patient had a long history of chronic infective sinusitis for which she had had radical surgery; she had suffered from bronchial asthma for six years, the disease being intractable for three, and had received two courses of ACTH therapy; she was hypertensive and had experienced psychotic disturbances. For a week before her death she had received daily injec-

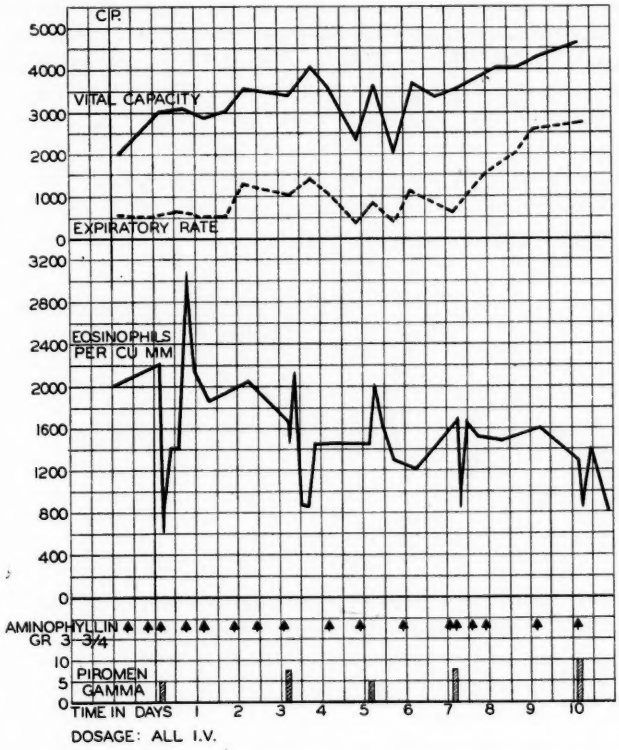

Fig. 3. A series of injections of Piromen in the same allergic individual as described in Figure 2 produced the above eosinophil response. Vital capacity and expiratory rate also are shown. Similar observations following treatment with ACTH, cortisone and concentrated adrenal cortex extract have been reported (Reprinted from Annals of Allergy, 8:626-640 (Sept.-Oct.) 1952, courtesy of Dr. Theron G. Randolph.)

tions of Piromen without displaying any toxic symptoms. It is well known that chronic intractable asthmatics may die suddenly, even after apparent improvement. It seems evident from the autopsy report that death was due to fibrinous bronchitis and may as readily have followed a drink of water as an injection of Piromen. The impression one receives from

this report is that the toxic effects of ACTH have been markedly minimized, while those supposedly caused by Piromen were grossly exaggerated.

Because Piromen is nonprotein, it is unlikely that it could cause anaphylactic-like symptoms unless it linked itself to some protein substance in the body to form a conjugate. This is improbable and has not yet been demonstrated.

The literature contains several reports on the use of Piromen in allergy and dermatitis.[16,20,24,29,40,41] This is a report of the author's clinical experience with sixty-three allergic patients treated with the drug. All but a few had previously received, without satisfactory result, conventional treatment such as avoidance measures, immunization and management of symptoms through the use of the usual antiallergic drugs. In all cases Piromen was used as adjunct therapy.

Evaluated results are shown in Table I.

TABLE I

	Total Cases	Excellent	Fair	Poor
Allergic Rhinitis	18	9	4	5
Atopic Dermatitis	6	5	1	
Bronchial Asthma	13	4	3	6
Hay Fever	9	4	2	3
Neurodermatitis	4	3		1
Seborrheic Dermatitis..	5	3		2
Urticaria with Angioedema	8	5	3	
Totals	63	33	13	17

Injections were given every three to four days when initiating Piromen therapy. Initial doses were low, ranging from one-half to one gamma, and were increased gradually until a clinical response was achieved. The response threshold varied from patient to patient and each required an individual dosage schedule.

The frequency of administration usually was reduced to one injection per week following the first three or four injections. However, in severe cases the three to four day frequency was continued. Both intravenous and subcutaneous routes were used with intravenous administration being the most effective.

Stubborn conditions such as bronchial asthma, allergic rhinitis and atopic dermatitis required more than one course of Piromen therapy to initiate or maintain a satisfactory response. The first course consisted of ten to fifteen injections and subsequent courses eight to ten injections. In no case was more than four courses employed. Courses were separated by at least one week of no injections. In those patients who showed no response after two courses, Piromen was discontinued.

The drug may initiate a febrile reaction when given intravenously.

Chills, slight fever, generalized aching and headache were noted in this series of patients. These side effects occurred within an hour after injection and were short lived. They occurred most frequently when dosage exceeded five gamma. No long term side effects have been noted to date.

In a few acute cases 25 mg doses of ACTH or cortisone were given to provide immediate relief. When Piromen was given concomitantly with the hormone, improvement was maintained after ACTH or cortisone was discontinued. In none of the few cases in which this combination was used was there exacerbation following the withdrawal of the hormone.

The following case histories illustrate clinical observations:

Case 1.—T. S., a man, aged forty-nine, had perennial and seasonal hay fever and asthma of ten years duration. Skin tests were positive to a significant number of inhalants and foods. An elimination diet was ineffective and desensitization over an eighteen-month period produced partial relief of seasonal symptoms only. Piromen was added to the regimen November 30, 1950, with a five-gamma intravenous injection which produced a chill. The dose was dropped to three gamma December 4, with no side effect noted. The patient received an injection every three or four days, the dose gradually being increased to 10 gamma by January 2. Six 10-gamma injections were given. Piromen was discontinued after fifteen injections and the patient allowed to rest for one month. Ten-gamma injections were resumed February 26, and eight were given at weekly intervals. At the end of this course of treatment the patient was 75 per cent improved. Piromen therapy was resumed June 30, and ten 5-gamma injections were given at three-day intervals ending September 2. At the end of this course of therapy the patient was symptom-free.

The patient had a recurrence in March, 1952, and seven 10-gamma injections were given at weekly intervals. At the end of this period the patient again was symptom-free. The patient was last seen February 20, 1953, and reported occasional nasal stuffiness but no other recurrence of symptoms.

Case 2.—M. K., a fifty-six-year-old woman, had had recurrent intractable bronchial asthma since 1945. Aminophylline, antibiotics, low sodium diet, elimination diet and sedatives did not prevent disabling attacks. She was hospitalized with a severe attack in November, 1950, and was relieved by ACTH. She suffered a recurrence two days after the hormone was discontinued and was maintained on conventional therapy until February, 1951, when she was given 25 mg of cortisone. She received cortisone periodically thereafter with only minor benefit. Piromen was added to the treatment program in September, with a 5-gamma intravenous injection. She received injections of 2.5 gamma twice weekly for a total of thirteen injections. No improvement was noted and Piromen was discontinued. The patient improved moderately on penicillin and now experiences periods of good feeling punctuated by asthmatic attacks. She was last seen in January, 1953, and had had no disabling attacks for the past six months.

Case 3.—M. R., a woman, aged thirty-eight, had allergic rhinitis of five years' duration. Elimination diet, liver and iron injections, and anti-allergic drugs for five months produced only partial relief. Piromen was added to the regimen in May, 1952. She received ten injections varying from 1 to 1.6 gamma per injection at weekly intervals, at the conclusion of which her symptoms were relieved. She was last seen in September, 1952, and reported no recurrence.

Case 4.—M. F., a man, aged twenty-five, had perennial and seasonal hay fever since March, 1951. Desensitization, avoidance measures and antibiotics produced little relief and a course of Piromen was begun October 21. Injections varying from one to two gamma were given weekly for ten weeks with some improvement noted.

Case 5.—E. D., a sixty-year-old woman, had had atopic dermatitis of the hands and face since age twenty-two. She was first seen after a flare-up in February, 1951. Skin tests were negative for foods, positive for sheep wool, house dust and gum tragacanth. Local therapy, desensitization and sedatives produced mild improvement. Piromen was started September 18, 1951, after seven months desensitization. She was started on 0.8 gamma intravenously, received 1.6 gamma, September 20; 1.2 gamma, September 21; 1.2 gamma, September 22; 2 gamma, September 24; 3 gamma, September 27; 4 gamma, October 1; and 7 gamma, thereafter every three to four days for two weeks. Pruritus disappeared after the fourth injection. Piromen was then given weekly until a total of twenty-one injections had been administered. At the end of that period the dermatitis was 90 per cent clear. The patient was last seen April 7, 1953, and the condition remains about the same.

SUMMARY AND CONCLUSIONS

1. Piromen, a *Pseudomonas* polysaccharide, was used as adjunct therapy in sixty-three cases of allergic disease including allergic rhinitis, atopic dermatitis, bronchial asthma, hay fever, neurodermatitis, seborrheic dermatitis and urticaria with angioedema.

2. Beneficial results were observed in 73 per cent of the cases.

3. Piromen may be given safely over long periods of time. It may produce a febrile reaction when injected intravenously in doses exceeding five gamma but no other side effects were noted.

4. When used as an adjunct, Piromen appears to increase the efficacy of concomitant therapeutic measures.

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THE VALUE OF PIROMEN IN THE TREATMENT OF ALLERGIC DISORDERS

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PIROMEN is a colloidal suspension of a polysaccharide derived from *Pseudomonas* species by tryptic digestion of the bacteria.[5] It has been isolated, and standardized by its ability to produce fever in test animals. It is said to be nontoxic and not allergenic.

In addition to its property of producing fever in microgram doses, Piromen has a number of interesting effects.[1,2,10] There appears to be general stimulation of the reticuloendothelial system, as shown by increased macrophage activity, and an increase in cellular elements in the spleen and lymph nodes. The adrenal glands of experimental animals show changes suggesting cortical secretory activity. In man, following intravenous injection of small amounts there is a leukopenia followed by a leukocytosis, and a relative or absolute eosinopenia.[6]

These blood changes in animals and man are reminiscent of the effects of ACTH, which led to the idea that Piromen might be useful in the treatment of allergic diseases.[1,6,7] This resemblance between the effect of Piromen and ACTH may be more apparent than real, since the eosinopenia that is produced by ACTH is essentially abolished by adrenalectomy, whereas that which follows Piromen is not.[8]

Previous studies on the clinical usefulness of Piromen in allergy[6,7,11,12] have been made with subfebrile doses of the pyrogen, in order to avoid the recognized effect of fever on disease and on the adrenal system.[4] In the study reported here we have tried to evaluate Piromen in allergy using subfebrile doses intravenously. Our purpose was to see whether Piromen could be used to replace other methods of treating allergies, or whether it would increase their effectiveness. A second purpose was to check other studies on Piromen, which differ widely in their conclusions as to the value of the material.[6,7,11,12]

METHOD

The subjects of this study were twenty-four patients from the Allergy Clinic of the Los Angeles County General Hospital, and fifteen patients from our private practices. They were selected at random from the group which had been treated for many months with only indifferent success,

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The Piromen used in this study was kindly supplied by Dr. R. P. Herwick of the Travenol Laboratories, Inc., Morton Grove, Illinois.

and who were not improving. The characteristics of these patients in respect to diagnosis or major complaint, associated complaints, duration of disease, and age features are given in Table I. Three-fourths of our subjects, or twenty-seven out of thirty-nine, were suffering from asthma with or without associated complaints. Only five of the twenty-eight had

TABLE I.

Major Complaint	
Asthma	14
Asthma with	
hay fever	7
bronchiectasis and/or emphysema	5
neurodermatitis	1
Total Asthma Cases	27
Hay fever and vasomotor rhinitis	3
Eczema or neurodermatitis	3
Urticaria and angioedema	3
Food Allergy	1
Allergic hydroarthrosis	1
Rheumatoid arthritis (with strong family allergy)	1
	39
Associated Complaints: Fatigue, migraine, vertigo, cough, angioedema, abdominal pain.	
Average duration of major complaint 12 years Age:	
Age spread	13 to 77
Mean age	42
Ages by decades	
11-20	5 pts.
21-30	0 pts.
31-40	9 pts.
41-50	13 pts.
51-60	6 pts.
61-70	4 pts.
71-80	2 pts.

well established permanent lung injury such as bronchiectasis and/or emphysema. The rest might have been expected to show great improvement did Piromen really control their asthma.

Uncomplicated pollenosis is not a common complaint in our clinic, so there are only three subjects in this category. These cases were treated during the spring months when symptoms usually are most severe.

Almost all of our cases were chronic, with twelve years for the average duration of major complaints.

The youngest patient was thirteen years old; the oldest seventy-seven. With the patients grouped by decades, five were in their teens, with none between twenty-one and thirty years of age. The relative freedom from symptoms during the third decade in allergic people is commonly seen in this area. The majority of cases were between thirty-one and fifty, with the peak in the fifth decade.

All injections were given intravenously, one, two or three times a week, using various amounts of a Piromen solution containing 10γ (gamma) per cc. The starting dose was 2 to 4γ as preliminary trials showed this amount was followed by a slight reaction but no fever. The amount injected was increased gradually according to the patient's tolerance.

Data on the Piromen dosage is given in Table II. The range of dosage was 1 to 24γ, with 90 per cent of the injections between 4 and 12γ. The average dose was 6γ. In all, fifty-three courses of Piromen were given to the thirty-nine patients, and eleven courses of placebo (buffered saline solution). These placebo injections were usually given after the patient

TABLE II. FEATURES OF PIROMEN DOSE

Range of dose used	1 to 24γ
Average dose (90% between 4 and 12γ)	6γ
Length of treatment	2 to 16 weeks
Average length	5.6 weeks
Weeks treatment Vs. No. of courses of Piromen	
2 weeks	5 courses
3 weeks	6 courses
4 weeks	15 courses
5 weeks	8 courses
6 weeks	7 courses
8 weeks	4 courses
9 weeks	3 courses
10 weeks	2 courses
12 weeks	1 course
16 weeks	2 courses
No. courses Piromen	53
No. courses placebo	11

had shown some improvement on Piromen. The length of any one course of Piromen varied from two to sixteen weeks, with the average at 5.6 weeks.

During the time Piromen was being given, patients were continued on their previous medication, if any. This consisted of desensitization injections weekly in the majority, together with various forms of aminophylline, epinephrine, ephedrine, iodides, antihistamines, sedation and occasionally antibiotic medications. For the most part these patients were taking medicine only when indicated. We felt that if Piromen were to produce striking benefit each patient would reduce the quantity of medications taken.

Patients were briefly interviewed at each visit, and more extensively from time to time. Response to Piromen was determined from questioning, physical findings, and the amount of palliative medication being taken. We were not able to make any measurements of lung function.

The changes in the leukocyte picture following Piromen was measured in eight patients and agreed with the findings reported by others.[1,6] Total eosinophile counts were taken before and three hours after 4γ of Piromen intravenously in three patients.

In six patients urinary 17-ketosteroids were determined as follows. On the first or control day excretion was measured from 7 a.m. to 7 p.m., and from 7 p.m. to 7 a.m. the following morning. Piromen was then given once or twice in the next six hours and ketosteroid excretion measured for the two consecutive twelve hour periods, 7 a.m. to 7 p.m. and 7 p.m. to 7 a.m. the third day. The absolute values of 17-ketosteroid output were recalculated as so much steroid per gram of simultaneous creatinine output. Since creatinine output is assumed to be constant with time, this can be used to compensate for any errors in ketosteroid collection.

RESULTS

A condensed description of all patients is given in Table III, and the results are summarized in Table IV. According to the benefit (or lack of it) from Piromen we have divided the patients into four groups: (a) worse while on Piromen; (b) no change; (c) temporarily improved, but relapsed while still on Piromen (or not responding to a subsequent course) and, (d) significantly and consistently better whenever taking Piromen. Ninety per cent of our patients had no real relief; 10 per cent did.

The four patients who became worse during Piromen treatment all had severe asthma of long duration; respectively six, fifteen, twenty-five, and fifty years. Each had 2+ and 3+ skin reactions to inhalants. One had no reaction to Piromen, two had moderate reactions (++) and the fourth developed angio-edema and giant urticaria immediately after her fourth and last injection of 2γ. Whether Piromen actually caused the asthma to get worse in these patients cannot definitely be stated since the group is too small.

The twenty-five patients who showed no change with Piromen do not need further analysis, and their characteristics and treatment can be seen in Table III.

Of the seven patients who were temporarily improved six had asthma and one urticaria. They had been ill for one and a half to twenty years. Five of them showed 4+ skin reactions to inhalants. During the first two or three weeks of treatment they "felt better" and were able to reduce other medication by 50 per cent to 75 per cent, although none was symptom-free. Five of these patients who "felt better" were switched to placebo after two or three Piromen injections, and each continued no better or worse. One was then released from treatment, and four were put back on the pyrogen. All gradually became worse, and increasing doses of Piromen had no beneficial effect. These patients had reactions ranging from none to severe (++++).

Four patients were consistently better on Piromen. Three had asthma, and one urticaria and fatigue. Their major complaint had been present from three to twenty-two years, showing no significant difference from the other group. All four had 3+ and 4+ skin reactions to inhalants. Two of them (patients Nos. 37 and 38) relapsed on placebo injections, but improved when Piromen was resumed. Dosage in this group was not different from the others, and reactions to the pyrogen were slight (+) to moderate (+++). Only one patient (No. 37, with urticaria and fatigue) was completely symptom free; the others continued to have mild asthma which was controlled satisfactorily with palliative medication. There seemed to be no way the good results in this group could have been predicted.

Data on reactions following Piromen are given in Table V. Chilly feelings, general malaise and tenderness of muscles were the most common complaints noted during forty of the fifty-three courses of Piromen. Arth-

TABLE III. PIROMEN PATIENTS

Patient Age—Sex	Chief Complaint	Piromen Dose & Duration	Reactions	Positive Skin Tests	Remarks
Group 1: Patients Worse on Piromen (4)					
1. L.B. f. 42	asthma 6 yrs.	4y/week 2 weeks	xxx	house dust 3x	Dust vaccine given one and one-half years with only fair relief. Asthma rapidly worse on Piromen. Refused to continue.
2. L.C. f. 20	asthma 15 yrs.	4y 2/week 3 weeks	O	house dust 3x pollens 2x wool 3x	Much worse during Piromen without usual aminophylline, sedation, etcetera.
3. M.H. f. 41	asthma 25 yrs.	(a) 4-12y 2/week 5 weeks (b) placebo 2 weeks	xxx xx	house dust 3x cottonseed 2x	Asthma progressively worse on Piromen, but better on Placebo. Given aminophylline, Potassium Iodide, sedation & dust vaccine.
4. H.J. f. 52	asthma 50 yrs.	6-2y weekly 4 weeks	x to xxx	orris 3x cat hair 2x	Slowly worse on Piromen. Hives and angioedema after last Piromen injection. Also has emphysema.
Group 2: Patients Showing No Change on Piromen					
5. A.A. m. 14	asthma 11 yrs.	2-4y weekly 2 weeks	x	house dust 4x pollens 4x	Course of Piromen may have been inadequate.
6. J.D. f. 54	asthma 5 yrs.	5-15y weekly 16 weeks	O	house dust 4x cow hair 2x	Also has eczema ear canals, hay fever and idiopathic epilepsy. Did best on dust vaccine and symptomatic medication. No difference between Piromen and Placebo.
7. N.F. f. 67	asthma 20 yrs.	5y weekly 8 weeks	xx	house dust 4x animals 3x pollens 2x	Also has hay fever. Patient thought severity of asthma less on Piromen, but no change in number of attacks or in medication needed. Checked for eosinophile response to Piromen.
8. E.G. f. 41	asthma 10 yrs.	4-8y weekly 6 weeks	xxx	house dust 4x pollens 2x	Refused to continue Piromen because of nausea, vomiting and severe malaise. Antihistamines and dust vaccine used. Also has hay fever.
9. M.G. f. 58	asthma 15 yrs.	(a) 4-11y 2xwk. 8 weeks (b) placebo 4 weeks	x	weed pollens 2x	Reduced medication on Piromen, but weather improved also. Got some relief later on placebo.
10. B.H. f. 44	asthma 10 yrs.	5-10y weekly 4 weeks	x	house dust 3x molds 3x pollens 4x	Some relief from desensitization and solution of emotional conflicts. Also has hay fever.
11. C.M. f. 52	asthma 10 yrs.	4-8y weekly 5 weeks	xx	house dust 4x pollens 3x	No improvement on Piromen. Later did better on desensitization. Also has migraine headaches.
12. N.M. f. 46	asthma 6 yrs.	4-10y weekly 9 weeks	xx and xxx	house dust 3x pollens 3x	Six months after first course of Piromen a single intravenous injection of 4y followed by mild shock-fainting, nausea, vomiting, collapse.
13. N.P. f. 20	asthma 7 yrs.	(a) 4-7y/week 4 weeks (b) 10y 2/week 5 weeks	x xx	house dust 4x danders 4x	Slight subjective improvement without objective evidence temporarily during second course Piromen. Strong emotional overlay. Also has bronchiectasis.
14. M.S. f. 31	asthma 2 yrs.	4-12y/week 10 weeks	xx	house dust 4x pollens 3x	Also has hay fever. Neither asthma or hay fever favorably influenced by Piromen.
15. S.W. m. 65	asthma 10 yrs.	4-24y/week 6 weeks	O	house dust 2x pollens 2x	No reaction even to 24y Piromen. Also has bronchiectasis and emphysema.
16. A.Z. m. 40	asthma 20 yrs.	3-10y 2/week 4 weeks	O	house dust 4x danders 4x molds 4x pollen 2x	Chronic sinusitis twenty years. Anaphylactoid reactions to asperin and penicillin. Chronic sinus infection.
17. B.G. f. 16	vasomotor rhinitis 2 yrs.	4-5y/week 4 weeks	xx	horse serum 3x cow hair 2x	Patient refused to continue Piromen. "Made her sick and did no good."
18. R.H. m. 37	vasomotor rhinitis 3 yrs.	2-10y/week 4 weeks	O	O	17-Ketosteroid excretion subject.
19. S.M. f. 72	hay fever 20 yrs.	4-8y/week 8 weeks	xxx	house dust 4x pollens 3x	No improvement on any treatment. Prominent allergic cough.
20. B.R. f. 45	hay fever 14 yrs.	5-8y 2xwk. 4 weeks	xx	pollens 3x danders 3x	Two previous polypectomies.
21. M.C. f. 17	eczema 17 yrs.	4-18y weekly 9 weeks	xx	house dust 4x feathers 3x pollen 3x wool 2x	Some improvement on local treatment and Piromen. Same after Piromen discontinued. Severe chills after 18y Piromen.

TABLE III. PIROMEN PATIENTS—CONTINUED

Patient Age—Sex	Chief Complaint	Piromen Dose & Duration	Reactions	Positive Skin Tests	Remarks
22. J.E. m. 31	neurodermatitis 2 yrs.	4-18y weekly 10 weeks	x	house dust 4x molds 4x feathers 4x	Severe bronchiectasis and asthma for fifteen years; 17-Ketosteroids measured.
23. H.J. f. 35	eczema 10 yrs.	4-10y weekly 4 weeks	xx	None	Better on local skin treatment and antihistamines.
24. E.K. f. 59	angioedema 2 yrs.	4-10y weekly 16 weeks	xx	None	Daily urticaria and angioedema not affected by Piromen. Antihistamines not effective.
25. J.R. m. 50	eczema 4 yrs.	4y weekly 3 weeks	xx	house dust 3x pollen 3x horse 2x	Piromen did not enhance effect of local treatment.
26. A.M. f. 41	food sensitivity 25 yrs.	2y weekly 4 weeks	xxx	dust 3x pollen 2x	Urticaria from B complex, sulfonamides, and foods; also colitis, fatigue. Severe malaise and chills from small doses Piromen.
27. L.H. f. 50	allergic hydroarthroses 15 yrs.	1-5y weekly 5 weeks	xx	None	Also has severe migraines. Remission induced by Cortisone not maintained on Piromen.
28. L.H. f. 68	arthritis 15 yrs.	1-5y weekly 4 weeks	O	None	Food and drug sensitivity. Remission induced by Cortisone; not maintained by Piromen.
		Group 3: Patients Initially Improved but Relapsed on Treatment			
29. M.A. f. 55	asthma 12 yrs.	(a) 2-5y weekly 8 weeks (b) placebo 4 weeks (c) 5y weekly 8 weeks	xx x x	house dust 4x	First month of Piromen reduced medication 75 per cent. Return mild symptoms; same on placebo; gradual relapse during second course of Piromen. Corpulmonale.
30. S.E. f. 50	asthma 35 yrs.	(a) 2-4y weekly 12 weeks (b) placebo (c) 4y weekly 8 weeks	x O xxx	None	Prominent emotional overlay. Reduced medication 50 per cent on Piromen. Held on placebo. No treatment three months. Relapse did not respond to second course Piromen.
31. M.G. f. 77	urticaria 2 yrs.	(a) 4-6y weekly 6 weeks (b) placebo 4 weeks (c) 6y weekly 8 weeks	x O x	None	Hives became smaller on Piromen then returned. No change on placebo or second course of Piromen.
32. A.L. f. 35	asthma 7 yrs.	4-2y weekly 9 weeks	xx and xxxx	house dust 4x pollens 2x	Also has hay fever. Reduced medication 50 per cent first three. weeks Piromen, then relapse Later better on desensitization alone. Severe reaction to Piromen six months later.
33. T.M. f. 37	asthma 10 yrs.	(a) 3-8y weekly 9 weeks (b) placebo 4 weeks (c) 2y weekly 6 weeks	xxx	house dust 4x pollens 3x	Also has hay fever. Moderate reaction to 8y Piromen. Better first three weeks, then gradual return of symptoms. Fatigue a prominent symptom.
34. E.S. m. 65	asthma 10 yrs.	(a) 4-6y weekly 5 weeks (b) 6-18y weekly 5 weeks	a) x b) xx	house dust 4x pollens 4x	Marked improvement from first course Piromen; recurrence not affected by second course. Severe emphysema.
35. P.W. f. 62	asthma 11 yrs.	(a) 4-6y weekly 12 weeks (b) placebo 4 weeks	a) x b) x	None	Reduced medication off and on during ten weeks then sudden return symptoms. No change on Piromen or placebo.
		Group 4: Patients Consistently Better on Piromen			
36. M.H. f. 46	asthma 22 yrs.	(a) 4-6y weekly 3 weeks (b) 10y weekly 7 weeks	a) O b) x	pollens 4x house dust 3x	No change on lower Piromen dose; reduced medication 75 per cent on higher dose; worse when Piromen not given.
37. I.S. f. 46	urticaria 5 yrs.	(a) 2-8y weekly 3 weeks (b) 5-12y weekly 3 weeks (c) placebo 2 weeks (d) 5-8y 2/week 2 weeks (e) 5-12y 2/week 2 weeks		house dust 4x pollens 3x	Fatigue prominent; symptoms abolished by each course of Piromen for two to three months. No relief from placebo. 17-Ketosteroid excretion measured.

TABLE III. PIROMEN PATIENTS—CONCLUDED

Patient Age—Sex	Chief Complaint	Piromen Dose & Duration	Reactions	Positive Skin Tests	Remarks
38. J.S. m. 31	asthma 8 yrs.	(a) 3-10y weekly 16 weeks	x	house dust 4x pollens 2x	Asthma started after pneumonia. Medication reduced 80 per cent on Piromen; relapse on placebo; again much better on Piromen.
		(b) placebo 4 weeks	x		
		(c) 6y/week 6 weeks	x		
39. N.V. m. 42	asthma 3 yrs.	(a) 3y/week 3 weeks	O	house dust 4x molds 3x	No change first course Piromen or placebo; medication reduced by 33 per cent during second course Piromen.
		(b) placebo 4 weeks	O		
		(c) 4-6y/week 6 weeks	x		

TABLE IV. SYMPTOM RESPONSE OF 39 ALLERGY PATIENTS TO INTRAVENOUS PIROMEN

Worse	4 (10%)
No change	24 (62%)
Temporary improvement but relapsed on treatment	7 (18%)
Improved during treatment	4 (10%)
	39

TABLE V.
REACTIONS TO INTRAVENOUS PIROMEN

Malaise	45
Chills	40
Arthralgia	17
Fever of 1° or less	10
Headache	8
Nausea	5
Severity of reactions	
O—(None)	12
x—(slight)	16
xx—(moderate)	17
xxx—(severe)	7
xxxx—(shock like)	2

Note: Total of reactions is greater than number of patients since many patients got more than one course of Piromen treatments.

ralgia was found in seventeen courses, mild to severe headache in eight, and nausea in five. The number of times a low grade fever was produced may have been greater, since our patients were not consistent in measuring this. Generally these effects would come on within two hours after the injection and last throughout the day. They could be fairly well controlled by aspirin.

There were two severe reactions that deserve comment. Both patients, (Nos. 12 and 32) had been on Piromen several months before without more than mild chills and malaise. A single dose of 4γ given to check eosinophile response was followed in a few minutes by faintness, pallor, tachycardia, sweating, nausea, abdominal pain and other signs of shock. Each recovered in an hour or so without supportive treatment, but did not feel well until the following day. Piromen is said to be non-anaphy-

TABLE VI.
URINARY EXCRETION OF 17-KETOSTEROIDS BEFORE AND AFTER PIROMEN

Patient	Material Measured	Time Periods*					Max. Temp.
		I	II	Piromen**	III	IV	
B.H. f 42	17-Ketost./24h.	8.7 mg.	6.1	4mcg.	5.7	7.0	99.0
Asthma	Creatinine	.55g.	.57	x2	.47	.60	
	17-Ketost./gram Creat.	15.8	10.7		12.1	11.7	
H.H. m 38	17-Ketost.	7.2	6.3	5mcg.	7.4	6.3	98.6
Asthma	Creatinine	.65	.58	x2	.63	.54	
	17-Ketost./gram Creat.	11.1	10.9		11.1	11.7	
J.E. m 31	17-Ketost.	3.8	5.2	8mcg.	3.1	5.7	99.0
Neuroderm.	Creatinine	.80	.78		.64	.71	
	17-Ketost./gram Creat.	4.75	6.6		4.84	8.03	
I.S. f 46	17-Ketost.	6.3	3.5	10mcg.	6.1	3.2	98.8
Fatigue	Creatinine	.84	.58	x2	.62	.69	
Hives	17-Ketost./gram Creat.	7.5	6.03		9.9	4.6	
R.H. m 37	17-Ketost.	11.7	3.8	10mcg.	6.3	5.5	98.6
Rhinitis	Creatinine	1.35	.055		.088	.091	
	17-Ketost./gram Creat.	8.7	6.8		7.2	6.0	
L.C. f 18	17-Ketost.	7.4	5.5	10mcg.	6.2	16.0	98.8
Asthma	Creatinine	.41	.84		.38	1.04	
	17-Ketost./gram Creat.	18.0	6.6		16.3	16.0	

*Time Periods: I. 7 a.m. to 7 p.m. first day.
II. 7 p.m. to 7 a.m. second day.
III. 7 a.m. to 7 p.m. second day.
IV. 7 p.m. to 7 a.m. third day.
**Piromen given at 7 a.m. start of period III and again at 2 p.m. if given 2x.
Max. Temp: Highest hourly reading during period III.

lactogenic, but these two cases suggest caution in its use after an interval from previous treatment. A fatal reaction which may have been due to Piromen has been reported.[9]

The "before and after" eosinophile response to 4γ of Piromen in the three patients checked for this was: (1) 170 to 69/cmm; (2) 130 to 207/cmm; and (3) 200 to 160/cmm.

The results of measurements on urinary 17-ketosteroid excretion before and after Piromen are given in Table VI. In only one patient (L.C.) was there any significant rise during the second twenty-four hours. This would indicate that these subfebrile doses of Piromen are not a powerful stimulus to the adrenal cortex. However, it may be argued that urinary 17-ketosteroids are not a sensitive indicator of short acting stimulation, and recent work indicates that circulating 11 dehydro-17 hydroxy corticosterone may be a much better index.[3]

DISCUSSION

We have not been able to show that intravenous Piromen in subfebrile doses has any specific effect on allergic disease. In this respect our experience is more like that of Samter and Kofoed,[9] who found Piromen no better than a placebo, than that of Wittich[11] or Randolph and Rollins[6] and Zindler.[12] The reports by the last three investigators state that Piromen produced relief of symptoms in the majority of patients with perennial allergy and food allergy. Yet both these reports give the impression that it was necessary to continue orthodox treatment along with Piromen, and that in many cases improvement was most noticeable at the start of Piromen treatment. In fact Randolph and Rollins state "uncontrolled food

sensitive individuals who obtained relief of their allergic manifestations early in the course of Piromen therapy may commonly have a recurrence of at least some of their allergic symptoms after a month or two of this type of treatment even though combined with specific inhalant therapy."[12]

Seven of our cases showed this type of response, that is, initial improvement in symptoms, followed in a few weeks by relapse to their former state despite continued Piromen treatment. We feel that this temporary improvement probably has nothing to do with any effect of Piromen on the antigen-antibody system, but is an example of the well known tendency of allergic patients to respond favorably but temporarily to any new and dramatic treatment. It was with this fact in mind that we tried to present Piromen treatment to our patients with as little discussion as possible.

It is true that one of our patients (No. 37) who complained of great fatigue repeatedly improved for a short time after a few Piromen injections. This relief of fatigue is mentioned prominently by other investigators.[6,12] But fatigue is a difficult symptom to evaluate, and its occurrence with vague gastrointestinal distress after eating certain foods is not a rigorous proof of an allergic origin. Until more information is available, we prefer to think that this effect of Piromen on fatigue does not operate on any antigen-antibody mechanism.

Our four patients who were consistently better on Piromen may have been benefited from a change in their immunologic status, but it is far more likely that this was the effect of mild "shock" caused by the injection of a foreign material. This would be in line with the benefit occasionally obtained in allergic disease from such nonspecific procedures as the intra-muscular injection of heated milk, pancreatic or leukocytic extract, blood or peptones. We believe that Piromen belongs in this category.

SUMMARY

1. Thirty-nine clinic and private patients with asthma, hay fever, eczema and other allergic diseases were treated with intravenous Piromen in subfebrile doses.

2. The average Piromen injection was 5γ, given once or twice a week, for an average of 5.6 weeks.

3. Four of thirty-nine patients (10 per cent) were consistently better while on Piromen, four (10 per cent) were worse, and thirty-one (80 per cent) showed no sustained change in symptoms.

4. Only one patient was actually free of symptoms for as long as two months after Piromen treatment.

5. Two severe reactions to low Piromen dosage (4γ) showed that it is not entirely without danger.

6. Piromen appears from this study to act in allergic diseases as a nonspecific foreign material.

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127 North Madison Avenue (Dr. MacLaren)

MOLD EXTRACTS AVAILABLE

The Hollister-Stier Laboratories now have available extracts of thirty-four species of atmospheric molds prepared according to the newly developed technique, and under license from the Association of Allergists for Mycological Investigation.

This newly developed technique, known as Method 33, will be supplied in the same strength (1:50) for scratch testing as has been used heretofore, but 1:100 will be the strongest strength of bulk extracts available for therapy or for further dilution and diagnostic work.

COMBINED ALLERGEN-CHLOR-TRIMETON DESENSITIZATION BY INJECTION

A Preliminary Study in Highly Sensitive Patients

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New York, New York

REACTIONS to allergic substances have in the past made it difficult to inject sufficient allergen to desensitize highly sensitive patients. Any method that would tend to reduce or eliminate local and/or systemic reactions would be worth while. The several attempts in this direction employed the technique of chilling the local site of injected antigen[2] and modification of pollen extract by emulsification in lanolin and olive oil[4] or by alum-precipitation.[7]

This report comprises seventy-three cases and is based upon the injection of an allergenic substance with Chlor-Thimeton, a well-tolerated antihistaminic drug. Other workers reported on pollen extracts[5] and antibiotics[3,6] in combination with this drug.

When Chlor-Trimeton Maleate injection* is mixed with the allergen, and the mixture injected subcutaneously or intramuscularly, the incidence of local and systemic reactions is appreciably reduced. Moreover, higher doses of the allergen can be administered in the desensitization process. Consequently, a better clinical response is obtained than with treatment using allergen alone.

DESENSITIZATION WITH POLLEN EXTRACT COMBINED WITH AN ANTIHISTAMINE

Desensitization of patients extremely sensitive to pollen, using a mixture of pollen extract with the antihistamine solution readily shows that the method prevents or controls systemic and/or severe local reactions caused by these allergens.

PROCEDURE

The solution containing the allergen is withdrawn into a sterile 1 cc tuberculin syringe, the quantity depending upon the dose to be administered. Into the same syringe is drawn 0.05 or 0.1 cc from a solution of the antihistamine (100 mg/cc).

The allergen and the drug are mixed in the syringe and the combined preparation is injected subcutaneously.

From the Department of Pediatrics—Director Dr. Horace Hodes, Pediatric Allergy Clinic, Dr. H. G. Rapaport, Physician in charge, Mt. Sinai Hospital, New York.

Some of the data was presented at the Scientific Exhibit of the American Medical Association in Chicago, in June, 1952.

*The Chlor-Trimeton Maleate injection (100 mg/cc) used in this study was supplied by the Schering Corporation, Bloomfield, New Jersey.

TABLE I. DESENSITIZATION WITH POLLEN EXTRACT AND CHLOR-TRIMETON BY INJECTION

	Group I		Group II		Group III	
Grading of patients with local and/or septemic reactions with allergen alone	++++		+++		++	
No. Patients*	15		30		7	
	Allergen Alone	Allergen with Chlor-Trimeton	Allergen Alone	Allergen with Chlor-Trimeton	Allergen Alone	Allergen with Chlor-Trimeton
Dose of Chlor-Trimeton		3-5 mg.		3-5 mg.		10 mg.
Average increase in dose of pollen extract allowed by addition of Chlor-Trimeton		No increase attempted		4.2 times		23.0 times
EVALUATION OF REACTIONS** TO ALLERGEN						
Degree	Moderate to Severe	Lesser Degree	Moderate to Severe	Lesser Degree	Moderate to Severe	Lesser Degree
Local Reactions						
No. Patients	15/15	6/15	30/30	15/30	7/7	0/7
Percent	100	40	100	50	100	0
Systemic Reactions						
No. Patients	10/15	0/15	13/30	1/30	1/7	0/7
Percent	67	0	43	3	14	0

*Allergic patients selected for their high sensitivity to allergen.
**Evaluation of reactions: Patients having one or more positive reactions were counted positive. The local reaction was read fifteen to twenty minutes after the injection.

ADVANTAGES OF THE PROCEDURE

1. Lessened Incidence of Side Reaction.

Local Reactions.—Only patients showing moderate to severe local reactions at the site of the pollen injection were selected for study. About 10 per cent of all allergic patients fall into this group. The combined preparation was injected into fifty-two patients with pollen allergy. The severity of local reactions was reduced or abolished in 58 per cent, as can be seen in Table I under "Evaluation of Reactions."

Systemic Reactions.—Some patients develop systemic reactions when receiving allergenic extracts for hyposensitization. Such reactions are greatly reduced or eliminated by the combined treatment (Table I). The addition of Chlor-Trimeton to the pollen allergen reduced the incidence of systemic reactions for all three groups from 46 to 2 per cent. The reduction of incidence for each group was: Group 1, from 67 to 0 per cent; Group 2, from 43 to 3 per cent, and Group 3, from 14 to 0 per cent.

2. Higher Doses of Allergen Tolerated.

The top or optimal doses of allergen tolerated by hypersensitive individuals can be increased many fold by the use of the combined preparation. With 3 to 10 mg of Chlor-Trimeton, the dose of pollen extract can be increased from four to twenty-four times more than that tolerated when administered without the antihistamine (Table I).

TABLE II. MIXTURE OF NON-POLLEN ALLERGENIC SUBSTANCES WITH CHLOR-TRIMETON

A. Prophylactic Injection of Chlor-Trimeton-Allergen Mixture

Allergen	No. Patients	Symptoms Caused by Injection of Allergen Alone	Dose of Combined Medication	Reactions from Combined Medication
Dust Allergen	3	Bronchial Asthma	3 to 10 mg Chlor-Trimeton with 0.3 to 0.5 cc Dust Allergen (1:2000)	No local reaction. No systemic reaction
Urographic Contrast Media	2	Urticaria	30 mg Chlor-Trimeton with 25 cc urographic agent intravenously	No systemic reaction. No side effects.
Crystalline Vitamin B 12	1	Allergic Rhinitis	2 mg Chlor-Trimeton with 30 mcg Vitamin B 12	No systemic reaction. No side effect.
Aqueous Procaine Penicillin	11	Urticaria	20 mg Chlor-Trimeton with 600,000 Units	2/11 Erythema and urticaria. No side effects.

B. Theraputic Injection of Chlor-Trimeton Alone

Allergen	No. Patients	Symptoms Casued by Injection of Allergen Alone	Dose of Chlor-Trimeton	Effects of Chlor-Trimeton
Penicillin	1	Angioedema, Urticaria	10 mg intra-muscularly for 3 consecutive daily injections	Excellent response
Urographic Contrast Medium	1	Urticaria	20 mg intra-muscularly	Urticaria subsided within 5 minutes and cleared in 30 minutes. No side reaction.
Urographic Contrast Medium	1	Severe dyspnea with cyanosis	20 mg intra-muscularly	Rapid recovery. No side effects.
Urographic Contrast Medium	1	Severe dyspnea with cyanosis	20 mg intravenously	Rapid recovery. No side effects.

3. Improved Clinical Response.

Improved clinical response for most of the patients in Groups 2 and 3 (Table I) followed combined injection of pollen extract and Chlor-Trimeton as the antihistamine. This permitted the injection of higher doses of pollen extract.

In patients of Group 1 no increase in the dose of pollen allergen was necessary. However, it was found helpful and desirable to mix the antihistamine with allergen to reduce the incidence of local and systemic reactions.

These findings suggest that desensitization procedures can be carried out more rapidly and effectively, and that they are better tolerated when Chlor-Trimeton-allergen mixtures are used rather than allergen alone.

COMBINATION OF OTHER ALLERGENIC SUBSTANCES WITH CHLOR-TRIMETON

Injection of a mixture of Chlor-Trimeton from 3 to 30 mg with other allergens, such as a dust extract, and with substances prone to cause allergic reactions, such as penicillin, vitamins and contrast media[1] avoided local and systemic reactions to these substances in fifteen of seventeen patients treated for an incidence of 88 per cent. (See Table II-A). Side effects are uncommon.

PROPHYLAXIS OF PENICILLIN SENSITIVITY

A mixture of 0.1 cc (10 mg) Chlor-Trimeton Maleate solution with 400,000 units of procaine penicillin in aqueous suspension was used by intramuscular injection. In a series of 897 unselected patients, 1,055 injections were made. Only one patient experienced a reaction, a mild generalized urticaria. This 0.1 per cent incidence of systemic reaction is unusually low and is in marked contrast to the higher incidence of reaction to penicillin alone, as reported in the literature.

THERAPEUTIC USE OF CHLOR-TRIMETON MALEATE INJECTION

Chlor-Trimeton by injection is useful in the treatment of patients with allergic reactions to penicillin or contrast media. Thus, 10 mg of the drug injected daily into the site of a large induration on the buttocks caused by penicillin in one case brought an excellent therapeutic response. The accompanying angioedema and urticaria cleared within three days (Table II-B). The antihistamine has also relieved moderate and severe systemic reactions following injection of contrast media. With 20 mg injected intramuscularly, urticaria was controlled within five minutes and cleared in thirty minutes in one case, the antihistaminic drug causing no side reactions. The effect of the antihistamine in relieving severe dyspnea with cyanosis following the injection of contrast media has been even more striking. With a dose of 20 mg of the drug intravenously administered, two patients have recovered rapidly and with no side reactions from the antihistamine.

DOSE OF CHLOR-TRIMETON

The dose of the antihistamine must be adjusted according to the response of the individual patient. An average dose of 5 mg of Chlor-Trimeton mixed with each dose of pollen or other inhalant allergen usually permits a gradual increase in the dose of allergen with tolerance by the patient. Chlor-Trimeton mixed with an allergen and injected subcutaneously at one site does not necessarily afford protection against a local or a systemic reaction from a simultaneous injection into a different site with another allergen not mixed with the antihistaminic drug. Therefore, 5 mg of Chlor-Trimeton should be mixed with each extract of allergen injected. With each intramuscular injection of penicillin, at least 10 mg and preferably 15 mg of the antihistaminic drug should be used. The minimum dose of Chlor-Trimeton to be used with contrast media intramuscularly has not yet been definitely established. In this study 20 to 30 mg of the antihistamine was used effectively.

Chlor-Trimeton in the doses employed in this study caused little or no local irritation or pain at the site of injection. Occasionally, a slight or moderate drowsiness lasting up to one hour followed the injection. If drowsiness is to be largely avoided, it is recommended that 10 mg

amphetamine sulfate be orally administered one-half hour prior to the injection.

Precaution.—A few patients may have systemic reactions to increased doses of allergen despite combination with Chlor-Trimeton. As a rule, these reactions will not be as severe as those following a comparable dose of allergen alone.

CONCLUSION

The incidence of local and systemic reactions occurring with injections of allergenic extracts in highly sensitive individuals is greatly reduced or completely eliminated by the addition of Chlor-Trimeton Maleate injection to the allergenic extracts. The same benefits accrue from the prophylactic injection of Chlor-Trimeton mixed with substances, such as penicillin and contrast media, that may evoke sensitivity reactions. The antihistamine can also produce relief from a severe local or systemic allergic reaction caused by the above substances mentioned.

SUMMARY

A study was carried out in unusually hypersensitive patients using Chlor-Trimeton Maleate injection to determine whether it (1) is non-irritating on the site of subcutaneous or intramuscular injection, (2) is well tolerated systemically and (3) affords protection against local inflammatory changes often caused by immunizing injections of allergens. It was found that Chlor-Trimeton Maleate injection fulfills these criteria. During the study, it was observed that the injection of the antihistamine (10 to 20 mg) with the offending allergens was largely protective against local as well as systemic reactions and through this protection larger immunizing and more rapid incremental doses in the desensitization procedure were permissible.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

THE ROLE OF ANTIBODIES IN THROMBOCYTOPENIC PURPURA

In a series of pioneer papers, Ackroyd[1] has demonstrated an immunological mechanism to be involved in thrombocytopenic purpura caused by Sedormid (allyl-isopropyl-acetyl-carbamid). If this drug is admixed to the serum of the sensitized patient, clot retraction is inhibited and the platelets are agglutinated or lysed. For lysis—but not for agglutination—the presence of complement is necessary. Similarly, agglutination of platelets by plasma has been reported in thrombocytopenic purpura following the administration of quinidine (Bigelow and Desforges[2]).

More recently, the presence of agglutinating antibodies versus platelets was discovered by Harrington et al[3] in twenty-one out of thirty-one plasmas from patients with idiopathic purpura, in the blood of four out of seven mothers who had delivered babies with neonatal purpura, and also in three of the babies involved. (The mothers themselves may or may not have shown signs of purpura.) Transfusions with blood or plasma from such purpuric patients caused a temporary decrease of circulating platelets in the "normal" recipient.

In these cases, no third agent is required in order to evoke platelet agglutination by the serum. This is in sharp contradistinction to the observations in purpura after Sedormid, when the presence of the drug is needed for the *in vitro* reaction. Harrington et al suggest that the sensitizing agent may combine with the platelets thus providing the specific combining group for reaction with the antibody. In idiopathic purpura, the agglutinin has the nature of an autoantibody or isoantibody.

The antibody is not necessarily a pan-agglutinin for platelets. When ten agglutinating sera were tested with over 100 platelet specimens, only eighteen reacted with every serum. The rest was clumped by none, one or several sera only. Thus, this series indicated a minimum of twelve immunological individualities ("types") of human platelets.

The case histories indicate that isoimmunization may play an important part both in idiopathic and neonatal purpura. All but nine of the thirty-one cases of idiopathic purpura presented a history of either having had blood transfusions or of having been pregnant. And all the babies with

1. Ackroyd: Progress in Allergy, III:531, 1952.
2. Bigelow and Desborges: Am. J. Med. Sc., 224:274, 1952.
3. Harrington, et al: Ann. Int. Med., 38:433, 1953.

the neonatal type of the affection were borne by mothers with previous pregnancies and/or history of transfusions. These data parallel those obtained in the "immunological" diseases affecting the erythrocytes.

In about one-third of the cases reported from St. Louis, no agglutinins versus platelets were found. Harrington and his colleagues discuss the possibility that sensitization to an undetected extraneous agent may be involved. If this were the case, the presence of this agent in the *in vitro* system would be needed, in order to demonstrate the antibody just as this was found necessary in the example of sensitization to Sedormid; a plausible working hypothesis. But it is tempting to speculate about the possibility that non-agglutinating ("monovalent") antibodies may be involved as is the case with iso-immunization to erythrocytic antigens.

In Ackroyd's cases of Sedormid purpura, a patch test made with the drug caused a reaction in the form of petechial hemorrhages. This raises the intriguing question as to whether the endothelial cells of the capillaries may be exposed to similar damage by an immune reaction as are the platelets.

The case of isoimmunization versus platelets represents one additional case, where antibody directed versus a constituent of living cell exercises a damaging effect when combining with its homologous antigen *in vivo*. But more and more evidence is becoming available that a deleterious result may ensue also, when antibody combines with antigen which is not a constituent of the living cell (though perhaps physically attached to it?). Striking examples of this are the reaction of platelets in Sedormid purpura as discussed above and the damage to leukocytes by reactions to proteinic antigens such as ovalbumin or tuberculin (see in this respect the recent paper of Waksman).[4]

1. Ackroyd: Progress in Allergy, III:531, 1952.
2. Bigelow and Desborges: Am. J. Med. Sc., 224:274, 1952.
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American College of Allergists Convention Echoes

PROCEEDINGS OF THE NINTH ANNUAL CONGRESS

The Ninth Annual Congress of the College was held at the Conrad Hilton Hotel in Chicago, Illinois, from April 24 to 29, 1953. Following the established custom of the College an intensive Graduate Instructional Course was held on April 24, 25 and 26. Thanks to the untiring efforts of Dr. Leon Unger, Chairman, and Dr. Morris Kaplan, Co-Chairman, the Instructional Course this year was a most comprehensive one and gave each man attending an opportunity to acquaint himself with the most recent trends in both diagnosis and treatment of allergies. The total registration for the Instructional Course was 233.

There were forty-five technical exhibits of products relating to allergy and allied subjects.

On Tuesday morning April 28, Dr. J. Warrick Thomas delivered his presidential address, followed by the guest speaker, C. M. Pomerat, Ph.D., Professor of Cytology, Medical Branch, University of Texas.

Following the guest speaker all members assembled in the ballroom for the annual business meeting. The following officers were elected and in due course assumed their respective offices and will serve until their successors are elected:

President—M. Murray Peshkin, M.D., New York, N. Y.
President-Elect—Homer E. Prince, M.D., Houston, Texas.
1st Vice President—Mayer Green, M.D., Pittsburgh, Pa.
2nd Vice President—Frank A. Simon, M.D., Louisville, Ky.
Executive Vice President and Counsel—Eloi Bauers, Minneapolis, Minn.
Secretary-Treasurer—Fred W. Wittich, M.D., Minneapolis, Minn.

Board of Regents—Three-year Term:

Jerome Glaser, M.D., Rochester, N. Y.
Morris A. Kaplan, M.D., Chicago, Ill.
Giles A. Koelsche, M.D., Rochester, Minn.

The present Board of Regents therefore consists of the following:

	Term Expires:
Harry S. Bernton, M.D., Washington D. C.	1955
Vincent J. Derbes, M.D., New Orleans, La.	1955
Jerome Glaser, M.D., Rochester, N. Y.	1956
Morris A. Kaplan, M.D., Chicago, Ill.	1956
Giles A. Koelsche, M.D., Rochester, Minn.	1956
Hyman Miller, M.D., Beverly Hills, Calif.	1954
Bret Ratner, M.D., New York, N. Y.	1954
Walker L. Rucks, M.D., Memphis, Tenn.	1954
L. Everett Seyler, M.D., Dayton, Ohio	1955
M. Murray Peshkin, M.D. *(President)*, New York, N. Y.	1954

Dr. Wittich, Secretary-Treasurer, presented a complete financial report covering the ANNALS OF ALLERGY for the year ending December 31, 1952. Dr. George E. Rockwell, Chairman of the Finance Committee, presented

a written report covering College finances for the year 1952, and this was supplemented by a complete certified audit report of the College.

Drs. Giles A. Koelsche and Fred W. Wittich presented a report on behalf of the Certification Committee.

Following the business meeting the annual meeting of the new Board of Regents was held in the suite of Dr. Peshkin. At this meeting several changes and amendments were made to the By-Laws so that Article V, Section 7, now reads as follows *(Changes are in italics):*

"(a) Number, election and appointment.—The officers of the College shall consist of a President, a President-Elect, a First Vice President, a second Vice President, *an Executive Vice President,* a Secretary-Treasurer, *a Counsel,* and such other or additional officers as the Board of Regents may from time to time designate and fix. *The positions of Executive Vice President and of Counsel shall each be an appointive office to be filled by the Board of Regents. The same individual may hold both offices.* All other officers shall be elected by the Fellows of the College at their annual meetings. If in any given year no annual meeting is held, the Board of Regents shall arrange for the election of new officers by mail vote. All officers shall assume their offices immediately following their election and they shall serve, *unless it is herein otherwise provided,* for a term of one year or until their respective successors are elected and qualify.

"(b) The President.—The President of the College shall preside at all regular and special meetings of the College and at all convocations for the conferring of Fellowships. He shall be Chairman of the Board of Directors during the calendar year immediately following his retirement from the office of President.

"(c) The President-Elect.—The President-Elect shall become President of the College at the expiration of his term as President-Elect.

"(d) The Vice Presidents.—Vice Presidents in the order of their seniority shall preside at all meetings of the College in the absence of the President.

"(e) The Executive Vice President.—The Executive Vice President shall not be a medical man, nor a fellow of the College, but shall, in fact, be a layman, preferably a lawyer. He shall exercise full and complete control over all its financial and business affairs and shall negotiate, supervise and sign any and all contracts and commitments made in its name or on its behalf. He shall exercise and carry out all such powers and duties, and shall observe all such directions and restrictions, as the Board of Regents may from time to time confer or impose upon him, and shall, in turn, be responsible to and report only to it and to the Board of Directors. As an Executive Officer of the College, he shall receive and be paid such annual compensation and salary as the Board of Regents may, from time to time, fix and determine.

"(f) The Secretary-Treasurer.—The Secretary-Treasurer of the College shall administer the funds of the College under the supervision of the Finance Committee, and he shall make such reports to the Finance Committee, the Board of Directors and the Board of Regents as may be required from time to time. He shall furnish a bond to the Corporation conditioned for the faithful performance of his trust. The Secretary-Treasurer shall keep the minutes of all meetings of the College, the Board of Directors, and of the Board of Regents, and all the standing committees; shall see that all notices are duly given in accordance with the provisions of the By-Laws; shall keep the records and the corporate seal and see that the seal is affixed to all documents requiring the same, and shall generally perform all duties incident to the office of Secretary-Treasurer, including such duties as may from time to time be assigned to him by the Board of Regents. The Secretary-Treasurer shall keep accurate reports of all members and their addresses with a record of attendance at meetings. He shall notify newly elected candidates of their election to membership. He shall submit the applications of candidates for membership to the Board of Regents, together with their qualifications for eligibility to membership. *He shall be an ex officio member of all committees and boards. He shall receive and be paid such fixed compensation or salary annually as the Board of Regents may, from time to time, fix and determine.*

"(g) The Counsel.—The man holding the office of Counsel shall be learned in the law and he shall give advice and counsel to the Board of Directors, the Board of

Regents, and to the several officers and committees on all legal questions from time to time arising. He shall be appointed and retained by the Board of Regents for such periods of service as it may consider proper and he shall receive and be paid for his services such compensation as the Board of Regents may from time to time fix and determine.

"(h) Consecutive Terms.—No officer shall hold office for two consecutive terms, except the Secretary-Treasurer, *the Executive Vice President, and Counsel.*

"(i) The Nominations of Officers.—The Nominating Committee shall be composed of five (5) members: the retiring president, two (2) members of the Board of Regents, and two (2) members of the College-at-large elected by the Board. It shall convene within twenty-four (24) hours after its selection; thereafter and not earlier than ninety (90) days but not more than six (6) months following its selection, the Nominating Committee shall select one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those selected. Any and all information contained in the membership records maintained in the Secretary's office as to any selectee shall, upon request, be seasonably supplied to the Committee. As soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary-Treasurer, provided said additional nominations are received in the office of the Secretary-Treasurer at least thirty (30) days prior to the next annual meeting. *Nominations may also be made from the floor at any annual meeting.* The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting.

"(j) Vacancies.—All vacancies among the officers of the College shall be filled by the Board of Regents. An officer elected to fill a vacancy shall serve during the unexpired portion of the term of his predecessor.

"(k) Board of Directors.—The general management of the Corporation shall be vested in a Board of Directors composed of five members as hereinafter provided who shall in turn vest the details of management in the Board of Regents. *The Board of Directors shall always consist of the following officers: the retiring President who shall be Chairman of the Board, the incumbent President, who shall be the Vice Chairman, the President-Elect and two Fellows from the College-at-large, neither of whom shall be a member of the Board of Regents and each of whom shall be elected to serve for a one-year term at the annual election of officers.*

"During the intervals between the meetings of the Board of Regents, the Board of Directors shall exercise all the powers of the Board of Regents in the management and direction of the business and conduct of the affairs of the College, except that it shall not have power to elect Fellows, to amend these By-Laws, or to regulate fees or dues of Fellowship. It shall keep a record of its proceedings and shall, immediately after each meeting, report the same to the Board of Regents for approval at the next succeeding meeting of the Regents. The Board of Directors may fill vacancies occurring in its membership through death or resignation. Directors filling such vacancies shall continue on the Board until the expiration of the term in which the vacancy occurred, or until the next annual election of Officers."

Article VI. Section 2, entitled "Finance Committee" has been amended to read as follows:

"The Finance Committee shall consist of three (3) Fellows elected by the Board of Regents. No member may serve for a period longer than three (3) years. Their terms of office shall expire in successive years so that, commencing annually hereafter the term of one old member shall expire and a new member shall be elected to succeed him. The Finance Committee shall be subject to the authority of the Board of Regents, and shall have the general supervision and direction of all the financial affairs and interests of the College. The Committee "shall have the power to invest and re-invest the funds of the College, to sell, transfer and convey any securities and property other than real estate, and to execute and deliver on behalf of the Board of Regents all necessary and proper instruments of transfer and conveyance. The Committee shall designate banking houses or trust companies in which the monies and securities of the College shall be deposited. The Secretary-Treasurer

shall perform such duties as may from time to time be specifically delegated to him by the Finance Committee. At each annual meeting of the Fellows, the Secretary-Treasurer shall present a statement and complete report of the financial condition of the College. At the close of each fiscal year the Finance Committee shall have the books and accounts of the College audited by a certified public accountant who shall make necessary entries and corrections, ascertain the cash and securities on hand, and furnish the Board of Regents in connection with the report of the Secretary-Treasurer a certificate of such accountant's findings."

Briefly, the principal effect of these changes in the By-Laws is this:

1. On and after the annual meeting in 1954 the Secretary-Treasurer will no longer automatically be a member of the Board of Directors. He shall, however, be an ex officio member of all committees and boards, which, of course, would include the Board of Directors.

2. The office of Assistant Secretary-Treasurer is abolished.

3. Two new offices are created—those of Executive Vice President and Counsel. Mr. Eloi Bauers of Minneapolis, who has been acting as Counsel for the College for a number of years past, was by unanimous action of the Board of Regents appointed Executive Vice President and Counsel to hold such office for a period of three years. No salary was fixed or agreed upon, but by resolution, also unanimously adopted, the Board of Directors was authorized, at its interim meeting to be held in Minneapolis some time during the month of November, 1953, to enter into an agreement with Mr. Bauers covering compensation due him, and fixing his compensation and the manner of its payment during the three-year term for which he has been appointed.

4. The Nominating Committee shall hereafter be composed of five members; the retiring President, two members of the Board of Regents and two members of the College-at-large elected by the Board. This Committee will convene within twenty-four hours after its selection but will not finally agree upon or announce the slate of its selection until a later date, and until and after it shall have had a chance to consider the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those selected, based upon information to be furnished from data on file in the office of the Secretary-Treasurer.

The Editorial Committee, consisting of Dr. Wittich, Chairman, and Drs. Ratner and Thomas, in accordance with the resolution under which it was created, submitted a proposed new Editorial Board set-up as part of its report. After lengthy discussion, the Board of Regents accepted the report, and in accordance with the recommendations contained therein, made appointments to the several positions, including that of Editor, by the appointment of the those men whose names now appear on the masthead of the current issue of ANNALS OF ALLERGY.

Dr. J. Warrick Thomas, as retiring President, is currently Chairman of the Nominating Committee, and the other members of the Committee selected by the Board are the following: Drs. L. Everett Seyler, and Walker L. Rucks from the Board of Regents, and Drs. Lawrence Halpin, and Harry L. Rogers from the College-at-large.

Dr. Morris A. Kaplan, aided by a most capable Local Committee on Arrangements, provided a superb floor show and entertainment for the guests assembled at the annual banquet, and their efforts were enthusiastically received. Complimentary recognition must also be given for the entertainment furnished to the ladies by a capable Hostess Committee, of which Mrs. Morris A. Kaplan was Chairman, Mrs. Leon Unger, Co-Chairman, and Mrs. M. Murray Peshkin, Honorary Chairman.

The Schering Corporation was host at a very fine cocktail hour immediately preceding the banquet, and we thank them as well as the Nepera Chemical Company which provided the sparkling Burgundy served during the banquet. Thanks is also due to the Chicago Society of Allergy for the

refreshments served to members and their wives on Monday and Tuesday, April 27 and 28, as well as to the following who also were contributors for entertainment and some scholarships for the instructional courses.

The Armour Laboratories	Chicago, Illinois
Almay, Div. of Schieffelin & Co.	New York, New York
Baxter Laboratories	Morton Grove, Illinois
The Borden Company	New York, New York
Bruce Publishing Company	St. Paul, Minnesota
Burroughs Wellcome & Co., Inc.	Tuckahoe, New York
Center Laboratories, Inc.	Brooklyn, New York
Ciba Pharmaceutical Products, Inc.	Summit, New Jersey
The DeVilbiss Company	Somerset, Pennsylvania
Doho Chemical Corporation	New York, New York
Dome Chemicals, Inc.	New York, New York
Duke Laboratories, Inc.	Stamford Connecticut
Graham Laboratories	Dallas, Texas
Greer Drug Company	Lenoir, North Carolina
Hollister-Stier Laboratories	Philadelphia, Pennsylvania
Hollister-Stier Laboratories	Spokane, Washington
Luzier's, Inc.	Kansas City, Missouri
Marcelle Cosmetics, Inc.	Chicago, Illinois
Chas. Pfizer & Co., Inc.	Brooklyn, New York
Ralston Purina Company	St. Louis, Missouri
Texas Pharmacal Company	San Antonio, Texas
Westwood Pharmaceuticals, Div. Foster Milburn Co.	Buffalo, New York

The officers and members of the College are deeply grateful to Dr. Giles A. Koelsche, Over-all Chairman and to all who in any way participated in or contributed to the success of the Ninth Annual Congress, and especially is this true in the case of the technical exhibitors and the Instructors who directed the Graduate Instructional Course.

The next annual congress of the College will be held at Miami Beach, Florida, from April 5 through 10, 1954. These dates will not in any way interfere with any of the holidays. Arrangements are already being made for an Instructional Course which it is likely will be held next year during each morning, and for Scientific Meetings which it is planned are to be held throughout each afternoon. Dr. Giles A. Koelsche, Consultant Physician, Division of Internal Medicine, Mayo Clinic, Rochester, Minnesota, will once again serve as Over-all Chairman of the Program Committee, with Drs. M. Murray Peshkin, President, and Fred W. Wittich, Secretary-Treasurer, as the other members of the Program Committee. It is earnestly hoped that Dr. Leon Unger of Chicago, who did such splendid work this year, will again make his services available as one of the chairmen of the Instructional Course. The chairman of the Local Committee on Arrangements has not yet been selected. There will be sections on Psychosomatic Allergy, Pediatrics, Dermatologic Allergy, Otolaryngology, and perhaps others, with, of course, luncheons and panel discussions.

Hotel arrangements have virtually been completed by Mr. Bauers, and it is expected that the Congress will be held at the famous Roney Plaza Hotel. The convention facilities of this air-conditioned hotel are in great demand for it not only affords excellent facilities for business sessions, commercial exhibits and scientific meetings, but its acres of luxurious and beautiful gardens provide ideal opportunities for real enjoyment and complete relaxation. Besides having one of the finest Olympic pools, the Roney Plaza has the largest private ocean beach in the entire Miami area, and it should provide the setting for a highly successful meeting in 1954.

FRED W. WITTICH, M.D., *Secretary-Treasurer*

REPORT OF THE COMMITTEE ON PSYCHOSOMATIC ALLERGY

Under the auspices of the Committee on Psychosomatic Allergy of the American College of Allergy, questionnaires were sent to the membership of the College in the fall of 1952.

The introduction to the questionnaire incorporated its purpose and read as follows:

Allergists are becoming increasingly interested in the significance of emotional factors in the precipitation and continuance of allergic disorders. Most of the discussions and publications have been concerned with diagnosis and recognition that worries about tensional personal problems can adversely influence bodily function.

Many of our members are saying: "I know that emotional disturbances can make allergies worse, or even bring on wheezing and itching, but what I really want to know is: in what practical way can I as an allergist and practicing physician help patients overcome such emotional difficulties?"

The sub-committee on Psychosomatic Allergy wants your advice on planning a program which will demonstrate the application of various methods of psychotherapy to some of the special problems which you may have in your daily practice.

Whether you favor using psychotherapeutic techniques or not, will you please answer the following questions and promptly mail this form in the enclosed envelope.

Returns on the Questionnaires:

Total number of questionnaires returned: 454.

Question 1: Do you find it helpful to use psychological techniques as an adjunct to physical diagnosis and treatment in your practice?

To this question—330 answered "Yes"
93 answered "No"
31 gave no answer

Question 3: Would you like to see and learn how other allergists actually apply psychological techniques in working with adults and children in an allergy practice?

To this question—433 answered "Yes"
17 answered "No"
4 gave no answer

In view of the interest shown by members of the College, Workshops were held on two successive meetings. The attendance at the Workshops and the nature of the questions brought up for discussion, made it clear that this type of teaching and investigation is desired by an important segment of the membership of the College. For this reason a similar plan will be followed in the 1954 meeting of the College.

I am indebted to the members of the Psychosomatic Allergy Committee for their co-operation during my period as Chairman. Especially noteworthy were the contributions of Dr. Dorothy Baruch, whose insight into the needs of the teaching program was exceeded only by her desire to apply her knowledge to help the development of psychosomatic allergies as a part of the College program.

To Dr. Boen Swinny, the new chairman of the Psychosomatic Allergy Committee and to Dr. Hyman Miller, the secretary of the committee, I should like to extend my best wishes for a successful tour of duty in this complicated field.

HAROLD A. ABRAMSON, M.D.

Progress in Allergy

BRONCHIAL ASTHMA

A Review of the Recent Literature

PHILIP M. GOTTLIEB, M.D., F.A.C.A., F.A.C.P.
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The extent of the interest in and study of bronchial asthma may be gauged from the fact that in the twenty-three months from January, 1951, through November, 1952, the Current List of Medical Literature included 611 titles under the heading of asthma. (A little more than one-half of these were in languages other than English.) They constituted about 0.32 per cent of the total listings. It is apparent that a review must be selective. The subject matter ranged from elementary summaries by medical students,[11] through informal reminiscences by pioneers in allergy,[139] to advanced immunologic, physiologic and clinical observations.

While the present review applies primarily to the medical literature of 1952, there has been no hesitancy in delving farther back when it seemed indicated, and a number of publications in 1953 are included. The emphasis has been clinically oriented. The most striking of the newer trends are concerned with the use of cortisone and corticotropin, with the increasing employment of pulmonary function tests both for the elucidation of the pathophysiology of asthma and for the evaluation of therapeutic methods, and with induced asthma for experimental and diagnostic purposes. The approaches are frequently combined.

The last review of bronchial asthma in the ANNALS (November-December, 1951) was a masterful summarization by Segal, Herschfus and Bresnick[236] on Physiologic Procedures in the Management of the Patient with Bronchial Asthma and Emphysema, the Effect of Bronchial Asthma and Chronic Pulmonary Emphysema on the Circulation, and the Pulmonary Function Tests in Bronchial Asthma. It is felt, therefore, that the present review will be of greatest value if all phases of asthma are considered.

Kahn[139] writes entertainingly of some of his early experiences. Among his interesting cases are the patient whose nocturnal asthma was due to bundles of the *Franseria tenufolia* form of ragweed used for making herb tea and stored directly over his bed. He also reports on a physician whose hay fever and asthma were virtually cured after three ant bites which resulted in a severe constitutional reaction.

A general summary of the clinical aspects of asthma as a refresher for the general practitioner appeared recently.[10]

This review will encompass the following aspects of asthma:

Incidence and Mortality
Pathology
Clinical Pathology
Etiology
Psychosomatic Factors
Experimental Asthma and Induced Attacks
Pulmonary Function Tests
Diagnosis
Differential Diagnosis
Treatment
Asthma in Children
Complications

INCIDENCE AND MORTALITY

Baldwin[15] pointed up the high frequency of asthma. In World War I, 7,797 patients with asthma were admitted to Army hospitals, accounting for about two in every 1,000 admissions. Over thirty years later, 3,318 veterans of that war were on the compensation rolls as service-connected cases of asthma, and another 4,806 were totally incapacitated and receiving pensions. In 1944, the U. S. Navy had 6,932 cases of asthma accounting for 470,090 sick days in that one year. As of June 30, 1950, the veterans of all services in World War II on the compensation rolls for asthma numbered 30,541. About 9,000 asthmatics die each year in the United States and asthma is the primary cause of death each year in over 2,000 instances. According to Williams[286] asthma is responsible for 0.6 per cent of all deaths in England and Wales; and for more than 1 per cent in the age group between thirty-five and fifty-five years. For the years 1930 to 1948, the death rate from this disease was 7.1 per 100,000 population, being slightly higher in males and lower in females. While the mortality rate from asthma has gradually fallen in the last twenty years, this is chiefly in the older age group, and for the ages of fifteen to twenty-four years has actually increased. The mean monthly prevalence rate for adults was found to be 904 per 100,000 population, giving asthma a rate several-fold that of tuberculosis, diabetes or rheumatic heart disease. In the armed forces of Great Britain, 0.9 per cent of the rejections were for asthma, placing it eighth in order of frequency. As a cause of civilian incapacity it is seventh on the total list, accounting for 206 of every 10,000 days of incapacity. Williams found that asthma accounted for 2.2 to 3.85 per cent of the medical admissions to several hospitals in South Wales; Bullen,[43] about 0.5 per cent in three hospitals in Rochester, New York. According to the latter, the death rate of hospitalized asthmatics was about 0.9 per cent. Since the years are not given, the influence of the newer therapeutic methods cannot be appraised.

Gardiner[95] and Spain and Fontana[244] listed some of the many occupations and occupational exposures giving rise to an increased incidence of asthma. Unger[257] studied forty-five farmers with asthma. More than half had positive skin test reactions to the dust of hay straw, barns, grain mills, hen houses, corncribs and oatbins. Other common offenders were pollens, molds, smuts, farm animals and house pets. Spain and Fontana[244] found that occupational asthma differs from other types only in the nature of the eliciting agents and the severity and tenacity of the symptoms, due to the intimate and overwhelming contact in confined areas. It is often associated with the nonoccupational form, and has an incidence no greater than that in the general population. While occupational exposure may be reduced by ventilation, isolation, and exhaust techniques, wet methods of work and the wearing of masks, it is almost always necessary to remove the worker to other surroundings or occupations. A valuable discussion of the medicolegal aspects with reference to Workmen's Compensation laws is included in their article.

PATHOLOGY

Bullen[43] studied the records of 176 asthmatics who died in three hospitals in Rochester, N. Y., in ninety-four of whom asthma was the primary or contributory cause of death. Autopsies were performed in 132 instances. In these fatal cases, the age of onset of the disease averaged much later than in most asthmatics—chiefly in the fourth to sixth decades

of life. In about one-half of the patients, death occurred within ten years after the onset of asthma, and in about one-fifth, within five years; nevertheless, nearly one-half of the patients lived into their seventh decade or longer. In but very few cases was specific sensitivity to foods, inhalants or drugs important; "intrinsic" or "bacterial" asthma seemed a greater threat to life. Morphine was used very little and was not a factor in causing death. Pneumonia and heart disease were the major causes of those deaths not due directly to asthma. Hypertrophy of the heart, with or without dilatation, was present in about one-third of all the cases. Many of the patients had used a great deal of epinephrine by injection or nebulizer; no pathologic sequelae attributable to it were found. The reason for the higher death rate in men (120 males compared to fifty-six females) was not obvious—the greater frequency of coronary artery disease and of arteriosclerotic heart disease constituting a partial explanation. Asthma *per se* was thought not to present a threat to the heart; when emphysema developed, heart damage was likely to follow.

Walzer and Frost[276] reported seventeen deaths in a period of eighteen months among 290 patients with a primary or secondary diagnosis of bronchial asthma at the Veterans Administration Center at Whipple, Arizona. Of these, death was directly due to asthma in five cases, or 1.7 per cent. Five autopsies are reported in detail with several excellent photomicrographs. Only one of the five patients had a true allergic asthma at the onset (at the age of twenty-two), but this became intrinsic prior to his death at the age of fifty-three. In the others, the asthma began between thirty-eight and fifty-five years of age and was considered intrinsic. None had received morphine, atropine or phenobarbital. Only one was in status asthmaticus at the time of death. Pulmonary emphysema was present in all the fatal cases, death occurred acutely, and autopsy revealed plugging of the bronchial tree with viscid tenacious mucus. Other findings included hyalinization of the basement membrane, hypertrophy of the bronchial musculature, and hyperactivity of the bronchial mucus glands. The therapeutic implications led the authors to favor "spaced dosage" of bronchodilator drugs, such as aminophylline (average dose 0.27 gram) and ephedrine (25 to 50 mg) throughout the day and night, along with sufficient potassium iodide given two or three times a day to ensure a liquid sputum. While bronchoscopy was precluded by the suddenness of the terminal episodes, suction via a tracheal catheter should be considered. However, the necropsy findings of widely distributed mucus plugs tenaciously adherent to the small bronchi indicated that such therapy would be unlikely to succeed.

An editorial[75] based on these last two papers re-emphasized the importance of mucus plugging of the bronchi in fatal cases, the poorer prognosis in "intrinsic" asthma possibly resulting from infection and more apt to occur in middle life, the necessity of not unduly suppressing the cough reflex by means of sedatives, and the rôle of chronic and acute infection. It still remains to be seen how effective cortisone and corticotropin may be in reducing the death rate from asthma.

The relationship between asthma and the diffuse collagen diseases was discussed by Gillespie and Poteliakhoff.[101] A thirty-six-year-old woman had asthmatic symptoms for two years and acute diffuse findings for only a few weeks before death. A marked blood eosinophilia and leukocytosis (2,500 and 17,000 per mm,^{3} respectively, about fifteen months before) rose to 15,500 eosinophiles and 35,000 leukocytes per mm^3 shortly before death. At necropsy, mixed pathologic changes including eosinophilic

polyarteritis, Libman-Sacks endocarditis, and other collagen abnormalities were found, as well as involvement of the bronchial structures consistent with asthma. The pathology illustrated the not infrequent overlapping of the diffuse collagen diseases. Churg and Strauss[51] reported on thirteen autopsies and two surviving cases of asthma with hypereosinophilia. The asthma began between the ages of seven and fifty-eight years, and only two patients had a positive family history. From a few months to ten years after the onset, intermittent fever and marked eosinophilia appeared. The duration of life thereafter ranged from three months to five and one-half years. One patient died in status asthmaticus, but in the others asthma abated or ceased with the terminal illness. Pneumonia, sinusitis, and erythematous and maculopapular eruptions occurred frequently. Peripheral neuropathy appeared in ten cases, joint involvement in four. At necropsy, renal and cardiac findings were common. The highest leukocyte count recorded was 60,000 per mm^3 of which 84 per cent were eosinophiles. The authors hold that periarteritis nodosa in patients suffering from allergic diseases differs histologically from other forms of periarteritis, and is more properly an allergic angiitis, essentially an allergic granulomatosis in connective tissue characterized by an eosinophilic infiltration.

CLINICAL PATHOLOGY

Blood eosinophilia greater than 15 per cent is relatively rare in adults with uncomplicated bronchial asthma, according to Klemola.[147] In a seventeen-year-old girl this combination, called by the author the "Rackemann and Greene syndrome," appeared, along with evidence of peripheral neuropathy and occasional urticaria, about ten months after the onset of the asthma. Parasites were ruled out. The circulating leukocytes reached 55,000 per mm^3 with 62.5 per cent of eosinophiles and subsequently 43,600 and 84.5 per cent, respectively. Fever was present for only two days. The asthma disappeared for a period of three months during the leukocytosis and hypereosinophilia. The unique feature of this case is that she remains in relatively good clinical condition after six and one-half years of observation, with eosinophiles ranging from 7 to 20 per cent. Muscle biopsy was not performed. Klemola warns that a diagnosis of eosinophilic leukemia should not be made in the absence of immature cells in the bone marrow and infiltrations into the viscera.

Eosinopenia was observed by Jennings[126] during severe paroxysms in two cases of asthma, although both ordinarily had a pronounced eosinophilia. Following stress, both showed a return to previous high levels. It appears that severe stress results in an eosinopenia far beyond that seen following the usual therapeutic doses of pituitary and adrenal hormones.

van Ufford[262] of Utrecht studied the bacteriology of the sputum in 244 asthmatics. Cultures in duplicate with special precautions to prevent nasopharyngeal contamination yielded chiefly α streptococci (91.8 per cent) and β streptococci (59 per cent). Other organisms, including pneumococci (1.2 per cent) appeared infrequently. Specimens were also taken between paroxysms to determine the organisms responsible for the chronic bronchitis in many asthmatic patients. Sputum cultures are of value, according to the author, as an indication for chemotherapy which he found most effective when β streptococci were recovered, to determine sensitivity of the bacteria to antibiotics, as a guide to autogenous vaccine therapy and in controlling its application, and in following changes in the bronchial flora in conjunction with exacerbations of the asthma.

The same author[266] found the erythrocyte sedimentation rate to be indispensable for finding low rates as an "allergic symptom" and elevated rates to warn of the presence of a primary or secondary focus of infection, or of an independent disease such as tuberculosis; and for following the course of asthma in relation to the appearance and subsidence of the infectious factor. The necessity for repeated determinations is obvious. In 930 asthmatics, the sedimentation rate was normal in 38.8, increased in 31.2, and decreased in 30 per cent. When the one- and two-hour readings are indeterminate, twenty-four-hour determinations are suggested. The Weltmann reaction can also be used to distinguish between the "purely allergic" form of asthma and that complicated by bronchial infection, according to the observations of Ruiz-Moreno and Bachmann.[218] However, in cases with chronic infection the Weltmann test often gives normal values.

Blood pressure levels,[264] basal metabolic rate,[263] fractional gastric analysis,[265] and blood sugar values[268] were determined by van Ufford in large series of asthmatics. Accepting 110 to 130 mm Hg systolic and 70 to 85 mm Hg diastolic as normal and in comparison with controls, 468 asthmatics had normal, 454 had decreased, and thirty-seven increased systolic and/or diastolic blood pressure.[264] There was no significant difference between those with infectious and those with non-infectious forms. He holds that functional hypotension may be responsible for fatiguability, weakness, sleepiness and the like, and may require therapy. Järvinen[125] of Finland, however, found hypotension (below 100 mm Hg systolic) in only 2 per cent of 528 asthmatic patients, and hypertension (above 160 mm Hg systolic) in 22 per cent. The discrepancy between his and van Ufford's figures may be explained in part by the differences in the standards accepted by them as normal.

In 420 cases of asthma, the basal metabolic rate[263] was increased (above +20) in 26 per cent and decreased (below —10) in 6 per cent. Normal values were found in the great majority. Statistically, those with marked blood eosinophilia tended to have thyroid dysfunction a little more frequently. Treatment of the thyroid abnormality never resulted in direct improvement of the asthma, but did give indirect benefits in decreased nervousness, improved sleep, weight gain, et cetera. In hyperthyroidism associated with asthma, the avoidance of epinephrine and the stopping of continuous potassium iodide therapy was sometimes beneficial. While not responsible for asthma, thyroid disease seems to affect it unfavorably.

In 100 asthmatics, 48 per cent had gastric achlorhydria or hypochlorhydria.[265] Of these, only eight patients had post-prandial gastric complaints. It is suggested by van Ufford that such cases be treated with both hydrochloric acid and pepsin. The relationship of the hypochlorhydria to asthma is discussed. Only one instance of peptic ulcer was found in 1,000 asthmatics. In the experience of this reviewer, peptic ulcer is not infrequent in asthma patients, and probably approaches the incidence in the general population. Glucose tolerance determinations[268] after the oral administration of 50 grams of glucose in 100 asthmatics revealed eight instances of low and twelve of high fasting levels; and abnormal curves in a considerable number, including twenty-three with unduly high curves. It is concluded that asthma and diabetes mellitus are not mutually exclusive. This is contrary to the earlier findings of Salgado Filko.[221]

Histamine and acetylcholine studies have not been neglected. Jiménez Díaz and his colleagues[133,134] of Madrid found that the blood histamine curves after the administration of histamine were the same in both normal and asthmatic individuals, and no increase in the histaminase activity of the

plasma was noted in the latter. Plasma histaminase values were markedly increased in anaphylactic shock. These studies are analogous to those of Rose et al[212] who compared the histamine content of arterial and of mixed venous bloods, the latter obtained from the right auricle, right ventricle, or pulmonary artery by means of intravascular catheterization. The use of arm vein blood for this purpose is subject to criticism. Control blood histamine values were higher than normal in asthmatics, and were higher in the arterial than in the mixed venous samples, unlike the normal individuals who showed little difference in this respect. There were no significant changes following the induction of asthma by the inhalation of ragweed pollen in two patients, or of asthma-like episodes in fourteen by the injection of histamine or mecholyl. These findings do not support the theory that histamine is a factor in the production of asthma, but are not considered sufficient to invalidate this theory.

The hypothesis that bronchial asthma represents an imbalance of the autonomic nervous system postulates either an increased amount of acetylcholine at the end organs or a disturbance in the cholinesterase enzyme system. Excessive amounts of acetylcholine have not been previously demonstrated in the blood or tissues of the asthmatic. Scudamore and his colleagues[230,231] determined the serum acetylcholine level in eight patients (two of them during paroxysms) and in fourteen healthy adults employing the isolated clam heart method. Half of the asthmatics had values above the upper range of the control individuals, and the remainder showed high normal levels. All were above twice the normal mean, and the differences were statistically significant. As previously reported by others the serum and erythrocyte cholinesterase levels in asthmatics were found to be in the normal range. It is thought that of the many factors involved in asthma, the release or accumulation of acetylcholine may play a significant rôle.

Schild and his co-workers[224] demonstrated that the isolated bronchial muscle from an asthmatic patient contracted at the first contact with dilute solutions of the specific antigens to which the patient was clinically sensitive. While desensitized by a single exposure, it would subsequently respond to another antigen. High concentrations of antihistaminic drugs, 10,000 times those required to antagonize histamine effects, prevented these responses. Moreover, isolated lung tissue and bronchi from asthmatic patients released histamine when brought into contact with the specific allergen. None of these findings were obtained with the bronchial muscle or lungs of non-asthmatic individuals. It was concluded that there is no essential difference between these phenomena and those of experimental anaphylaxis in animals, as exemplified by the Dale experiment; and that histamine release and contraction of the bronchial muscle play a definite part in allergic asthma. Rosa and McDowall[211] performed similar experiments, but employed specimens obtained at thoracic surgery, including one from a miller with flour asthma subjected to a pneumonectomy for bronchogenic carcinoma. They found that isolated human bronchi react like those of the guinea pig rather than the rat or rabbit. They are constricted by histamine and acetylcholine; these contractions are relaxed by antihistamines and atropine, respectively, and both by epinephrine in very high dilutions. A histamine-like substance is released on applying the antigen to isolated sensitized bronchi, but also by dissection of the preparation.

Järvinen[125] found no evidence of impairment of adrenocortical function as far as mineralocorticosteroid and glucocorticosteroid functions are concerned in a series of patients who had had asthma for an average of 10.7 years. In twenty-two cases restriction of the daily sodium chloride intake

to 2 grams or less for periods of eight to ninety-five days had no clear effect on the disease. Exposure to low atmospheric pressure during paroxysms in four cases had the effect, despite aggravation of the anoxemia, of partially relieving the symptoms. Desoxycorticosterone acetate in daily dosage of 5 to 50 mg for two to fourteen days gave no clear-cut results: a favorable effect in three cases, perhaps some benefit in three, no change in eight, and exacerbations in two. Turiaf and Scholler[254] had previously shown that the combined administration of desoxycorticosterone and ascorbic acid did not influence asthma.

ETIOLOGY

The significance of heredity in asthma was investigated by Schwartz[228] of Copenhagen by means of a careful statistical analysis by the Weinberg proband method of the medical histories of the relatives, living or deceased, of 191 patients with asthma, fifty with baker's asthma, and 200 control subjects. His lengthy monograph presents extensive statistical tables. He concluded that bronchial asthma is a hereditary disease regardless of whether or not it is of definitely allergic origin. A genetic relationship exists between asthma, allergic rhinitis, neurodermatitis (Besnier's prurigo) and, presumably, hay fever. In all probability, the mode of inheritance is by Mendelian dominance with failing manifestation, depending on the genotypic environment (polymerism). There appears to be a genetic "localization factor" in asthma. Extrachromosomal inheritance seems unlikely. Exposure to an allergen appears to play a subordinate rôle in the development of the disease, influencing mainly its clinical manifestations. Baker's asthma is shown to be due to an inherited predisposition to asthma in general. Contrary to general belief, no genetic relationship was found between asthma (or allergic rhinitis) and dermatitis, migraine, urticaria, angioneurotic edema, gastrointestinal allergy, and certain other diseases.

The etiology and pathogenesis of asthma has recently been discussed in the broadest sense by Rackemann[205] with emphasis on depletion, by Prickman[199] with emphasis on secondary bronchitis and the management of complications, by Alexander[3] with reference to nonallergic asthma, and by Curry.[63] The last-named felt that the relative rôles played by bronchospasm, edema of the bronchial mucosa, and hypersection is not clear, and may differ in allergic asthma and that following infection. Many attacks are not allergic and histamine may be an important factor. He considered the influence of the autonomic nervous system which plays an important, but at present not clearly delineated, part; the endocrine system about which there is much speculation and little factual data; metabolic disturbances affecting hydration, sodium, potassium, and calcium; infection, which is important in precipitating attacks but without clear evidence of bacterial allergy or of the rationale of the use of bacterial vaccines; and psychiatric factors, perhaps operative by reason of hyperventilation.

From such widely separated locales as southern California and South Africa, Small[241] and Ordman[188] report increasing numbers of cases caused by the inhalation of caster bean (*Ricinus communis*) dust. Exposure is largely occupational, resulting from the pomace used as a fertilizer. Ordinary intradermal and even scratch tests may be unsafe, and puncture tests are preferred by Small. Occupational asthma due to wood dust (complicated by spontaneous pneumothorax) in a carpenter was reported by Blumenthal,[28] due to paraphenylenediamine in furriers by Tara et al.,[251]

and to tung nut in a chemist by Macaulay.[162] Tung nut oil is used in making lacquers and paints. Chafee[48] redirects attention to rat and mouse danders as offenders, with one case exposed at home, the other in a factory. Passive transfer was positive, and hyposensitization effective. One may wonder if rodent hair sensitivity may not explain some otherwise obscure cases. Marconi and his colleagues[166] found a high incidence of asthma and other allergic states in the workers in silkworm factories in Italy, attributing it to the hairs and scales of the silkworm moths and obtaining positive reactions with the moth "dust."

That such relatively simple chemical compounds as ammonium chloroplatinate [$(NH_4)_2$ $PtCl_6$] and chloroplatinic acid may be responsible for asthma was demonstrated in Switzerland by Jordi[137] and in South Africa by Marshall.[169] Positive skin tests were obtained.

Gyllenswärd[106] described the startling case of a ten-month-old boy whose severe asthmatic paroxysms occurred only in the presence of his mother and *only* during or just prior to her menstruation. Deliberate exposure to other menstruating women had a similar effect. Hyposensitization with an extract of menstrual discharge in Coca's solution was successful. He attributed the sensitivity to the menotoxin, a euglobulin.

Recent reports have elucidated some of the features of mold allergy. Cadrecha Alvarez and Fernandez Castro[45] employed a modification of Feinberg and Steinberg's pollen counting method to obtain hourly fungus spore cultures in Havana. Their previous studies had yielded the largest number of colonies on days and in that portion of the day when the wind velocity is increased. While mold-sensitive asthmatics may be worse at windy times, they also usually have an exacerbation of symptoms, independently of the wind, in the early evening and at night. With their new technique, eliminating the influence of air motion, they demonstrated the highest atmospheric concentration of mold spores at night, after 6 p.m., corresponding to their clinical observations. Of course, their findings apply only to Havana. No effort was made to count nonviable mold spores. Swaebly and Christensen[249] isolated up to 3,000,000 mold colonies per gram, with an average of 179,966 mold colonies per gram, in various house dust samples from homes in Saint Paul and Minneapolis. Molds were present in some numbers in samples of new furniture stuffing and in considerably greater numbers in used materials. Foam rubber appears to be somewhat susceptible to invasion by molds, though to a lesser extent than certain fibers. The molds in the air within homes (chiefly *Penicillium* and *Aspergillus*) may differ in both kind and numbers from those in the outdoor air (predominantly *Alternaria* and *Cladosporium*) at the same time. The number of viable mold spores in the air within homes may fluctuate sharply during a single day, apparently in connection with physical activity and sweeping. Maunsell[171] found the predominant genus of mold in the air of seven of eight homes in the London area, in the months of November to March, to be *Penicillium*. The total number of colonies recovered by the sedimentation technique increased approximately fourteenfold during the raising of dust, and was still approximately fourfold higher shortly thereafter. This rise was mainly due to increases in the number of colonies of Yeast. *Pullularia*. *Penicillium*, and *Cladosporium*. The deficiencies of sampling by the sedimentation technique are properly emphasized.

Keeney[143] reported a case of *Candida* asthma, with roentgen evidence of peribronchial infiltration. Cultures of sputum and of scrapings from white plaques on the gums yielded *Candida albicans*. Skin tests with one protein

and two carbohydrate fractions from a *Candida* broth filtrate gave immediate wheal and marked delayed reactions. The passive transfer test produced immediate positive reactions. Therapy with a sodium caprylate aerosol was effective in about four weeks. Ordman[189] observed a case whose asthma was related to a particular mattress used on a camping trip. Cultures revealed *Mucor, Penicillium,* and *Fusarium,* and these gave markedly positive skin tests. The present reviewer once observed the occurrence of a virtual "epidemic" of bronchial asthma, affecting nearly one-fourth of the occupants of a rather damp barracks. Several mattresses yielded a pure culture of *Aspergillus nigricans.* Intradermal tests were confirmatory, and a change of mattresses obviated the symptoms. Frankland and Hay[87] of London present evidence that the fungus causing "dry rot," *Merulius lacrymans* may be responsible for asthma. It is particularly common in bomb-damaged homes. While it sporulates from August to October, the spores are present in the dust all year, and are carried by convection currents through the cracks. Seven of forty-eight asthmatics had positive prick tests with an extract of dry rot spores, and six of twenty gave positive intradermal tests. Intentional inhalation of the spores by a known sensitive patient could induce asthma at any time.

Salén[220] again draws attention to the allergenic significance of lycopodium, the spores of the moss, *Lycopodium clavatum* of the fern species. Exposure is largely occupational, in theatrical and pharmaceutical personnel. However, metal molds, fireworks and dry shampoos also contain this substance, and there may be hazard from the plants themselves in some localities, at least in the Scandinavian peninsula. Provocative exposure trials were positive in twenty-seven cases, many positive transfer tests were obtained, and specific hyposensitization was successful in eleven cases.

Based somewhat on a report of Schonwald and Deppe in 1948, the hypothesis is advanced by Dutton[73] that air-borne nonpathogenic bacteria are a factor in certain allergic problems. Many patients have exacerbations of asthma and/or hay fever incident to periodic dust storms in the semi-arid Southwest. At such times the number of air-born bacteria increases about 100-fold. Bacterial suspensions prepared from culture plate exposures gave immediate positive skin tests, sometimes in very high dilution, in about 80 per cent of such cases, but in only about 5 per cent of the allergic patients not reporting such flares. The author gained the impression that clinical improvement followed treatment with such vaccines in about one-half of seventy-five patients, although all were receiving other therapy. In a few such subjects, deliberate but cautious overdosage resulted in exacerbations. Dutton is clearly aware of the tentative nature of his conclusions, and outlines the many technical problems posed. This provocative hypothesis may prove to be clinically important, but one cannot help speculating as to its significance in non-arid areas.

Aspirin sensitivity was demonstrated in twenty-two cases (2.7 per cent) in a series of 830 successive asthmatic patients by Walton.[274] Five of them died within one year, confirming the impression of the poor prognostic import of aspirin allergy. In contrast to previous reports, most of the patients had positive skin tests to other allergens. Females predominated in a ratio of 2:1. The key chemical grouping appeared to be the acetyl radical, and sodium salicylate was tolerated. Anaphylactic shock with asthmatic manifestations resulting from the intravenous administration of thiamine chloride was reported by Armanino and Scott.[6]

The significance of food allergy as a cause of asthma is discussed by Walter[273] on the basis of three cases due to only this cause, along with

two others in whom food sensitivity complicated inhalant allergy. He states that many so-called cases of intrinsic asthma can be relieved by correctly diagnosing their food allergies and completely eliminating the incriminated foods from the diet. Mendez and Hughes[174] described a case of asthma due to beef, with positive skin tests to a tryptic digest of beef muscle at 30° C. and to commercial meat extractives (Marmite and Oxo), although tests with extracts of undigested meat were negative.

Opinions still differ regarding the incidence and importance of infectious factors in asthma, the location of the foci, and the age group predominantly affected. Flensborg[84] found that much of asthma in the first three or four years of life follows respiratory infection. In 450 cases, the onset of asthma was preceded by frequent colds in 55 per cent, by acute laryngitis (pseudocroup) in 33 per cent, by pneumonia in 9 per cent, and by measles or pertussis in 16 per cent. Skin testing with bacteria gave many late tuberculin-type reactions, but these also occurred in nonallergic children with frequent respiratory infections and hence were not diagnostic. In comparing groups of asthmatic children reactive to bacteria with those insensitive, no significant differences were found in the blood eosinophilia, family histories or sinus roentgenograms. However, infantile eczema was about three times as common in the former group. The elimination of foci of infection and treatment with autogenous and stock vaccines produced excellent results (81 per cent being free of asthma or much improved)—better, in fact, than those obtained by desensitization of "real" allergy. The production of asthmatic constitutional reactions by injections of vaccines, usually on the second day after treatment and sometimes after as few as 10,000 bacteria, is thought to be conclusive evidence of bacterial allergy.

Davison[65,66] studied by bronchoscopy and otherwise, twenty-five asthmatic adults, all with suppurative bronchitis. Bronchiectasis was also present in four, Loeffler's syndrome in five, and chronic suppurative sinusitis in thirteen cases. He holds that asthma appearing after the age of forty is usually due to infectious bronchitis and represents a tuberculin type of bacterial allergy, which in turn is responsible for the chronicity of infection in both the upper and lower respiratory tracts. Bronchiectasis is thought to be preventable by vigorous penicillin and streptomycin therapy of acute bronchopulmonary infections in allergic patients. According to Kourilsky and his co-workers,[151] the onset of asthma is often caused by an infection of the submucosa while chronic asthma with profuse expectoration is always due to superimposed infection. The infection preceded the asthma in twenty patients, and was concurrent in three, secondary in four, and absent in one. Only ten had normal sinuses. Infection was present in the gums and teeth of some, and mild rhinopharyngeal infection preceded relapses in others. Bronchoscopy revealed that the bronchial mucous membranes were red, congested and dark. Bronchial biopsy proved bronchial inflammation that was not detected clinically or bronchoscopically. These findings correspond to those of Dubois de Montreynaud,[72] outlined below. Infection as the main cause of asthma becomes increasingly important in the older age group, according to Kourilsky.

Chobot[50] believes that infection is the most important single cause of asthma in children, often in conjunction with inhalant allergy. The foci in children are usually in the tonsils and/or adenoids, or in recurrent tissue after surgical extirpation; in adults, sinus and dental infection are the usual allergic causes. The removal of infected tissue prior to the onset of severe asthma serves to prevent serious trouble and constitutes a most

important phase of preventive allergy. Surgery is avoided when the patient is over fifty years of age, has had asthma for more than five years, or has marked emphysema. Local radium applications to the nasopharynx are effective when the infected tissue is small and localized. The diagnosis of bacterial allergy is difficult and skin tests are valueless. Tuft[252] minimizes the importance of focal infection in the paranasal sinuses. Hyperplastic sinusitis is more often the result rather than the cause of the allergic processes. Radical operations should not be done unless extensive suppuration cannot be controlled by antibiotic and other therapy. Before assuming that asthma may be due to bacterial allergy, every effort should be made to find a nonbacterial factor or, if not successful, to treat the patient as though it were nonbacterial. Vaccines, stock or autogenous, especially those from bronchoscopic aspirations, may be useful adjuncts when employed in small doses, and preferably by the intracutaneous method.

Tuberculous infection is important in the pathogenesis of asthma in a very limited number of cases according to Mallen[163] of Mexico. Asthmatics did not give a significantly higher percentage of positive tuberculin tests, as compared to a nonasthmatic group, and their reactions to quantitative tuberculin testing showed no evidence of hyperergy.

According to Overholt, Walker and Woods,[192] hidden or unsuspected bronchiectasis is often present in the chronic asthmatic patient. Of seventy-six patients classified as "medical failures," bronchography revealed bronchiectasis in twenty-seven, of whom thirteen had the disease bilaterally. Resection of the diseased tissue was performed in all of the cases but one. Twenty of the patients were greatly improved in health; only seven required bronchodilator drugs after surgery. Two patients suffered infectious complications postoperatively and were not improved. The presence of bronchiectasis in an asthmatic person is thought to be of grave concern, no matter how small the involvement. The constant irritation of the bronchi with cough and purulent or bloody secretions constitutes an abnormal stimulus that eventually causes bronchospasm; the coexistence of bronchospasm and bronchiectasis forms a vicious cycle, each aggravating the other. The characteristics of the bronchiectasis may be masked by the paroxysms of asthma. The interrelated abnormal mechanics of the two conditions and the diagnostic problems are discussed. Turiaf, Rose and Marland[253] also reported the association of bronchiectasis with asthma. Friedman[88] and Waldbott[272] took vigorous exception to Overholt's criteria for the diagnosis of asthma, and to his implication that bronchiectasis is not uncommon in asthma. The problem appears to be, in some degree, one of semantics. A rational discussion in an editorial[76] pointed out that there can be evidence of bronchoconstriction in portions of the lungs not involved by the bronchiectatic cavities. In some cases of chronic infective bronchitis, the symptoms and signs of asthma and of diffuse bronchiectasis may be combined to such a degree that diagnostic classification is a matter of opinion. The decision as to which cases may be expected to be helped by lobectomy is difficult. Ill-considered surgery is to be deprecated, but more intensive efforts at detailed diagnosis is indicated.

Climatic conditions markedly influence asthma, according to Frouchtman[90] and Wildführ.[284] Cruz Auñón[62] followed 1,300 Sevillian asthmatics for eleven years, and found that humidity and atmospheric pressure have little effect on paroxysms, while the atmospheric temperature, and particularly its fluctuations, have a pronounced influence. Climatic conditions may affect the passage of allergens through the barriers of the body, may favor the appearance of certain allergens in the air, or may act on the

antibody-forming cells or shock tissues. Criep and Hammond[61] studied the geographical, meteorologic and air contamination factors pertinent to asthma in the Pittsburgh area. Changes in barometric pressure and air temperature, humidity, fog, storms and air turbulence all seemed to play a part. Climatotherapy must be individualized and is of unquestionable value in selected cases. Similar studies should be helpful in other areas.

PSYCHOSOMATIC FACTORS

The recent literature is replete with reference to the psychiatric aspects of asthma and its psychotherapeutic management.[1,37,54,55,74,215,279,285] It is probably not unfair to say that little has been added to the formulation of French and Alexander in 1941. The temptation to quote from Prout[201] cannot be resisted: "One outstanding conclusion is that while psychiatry has gone far in the understanding of these patients with bronchial asthma, it has done far too little in the way of relief." Many different approaches have been utilized. Wergeland[279] has employed psychoanalysis. He found that while character trends precede the first attack of asthma in children, they are also apt to be fostered by the asthma itself, thus establishing a vicious cycle. The patients' mothers are predominantly overprotective, mostly as a reaction to deep-seated hostility or complete rejection of the child. Basic emotional conflicts were shown to make the patient less resistant to the provoking allergens.

Projective psychological tests such as the Rorschach test and the Thematic Apperception Personality tests were applied by Mansmann[164] in twelve cases of asthma. Features found common to all the patients were: (1) some form of dependency expressed mainly by oral conflict; (2) emphasis on intellectual accomplishments and marked strivings for recognition and prestige; (3) psychosexual immaturity and incomplete acceptance of the rôle in life; and (4) women tend to have masculine identifications and men lack this identification. One of his patients could have the paroxysms relieved or induced by hypnosis and suggestion; there was no effect on the positive skin tests. Stevenson[248] showed that bronchial secretions are increased in association with feelings of anxiety and resentment evoked by discussions of painful life situations. In a psychosomatic study of 129 asthmatics, Schwoebel[229] found some psychogenic component in all: thirty-six spontaneously reported emotional experiences as the precipitating cause of their first attack and twenty-eight others recalled such during the anamnesis; seventy-eight stated that subsequent paroxysms were precipitated by conditions of psychogenic character. Prevalent character traits included fear, deep-seated anxiety, egocentric tendency, feelings of insecurity, unusual attachment to mother or equivalent person, irritation and moodiness. Throughout the literature, the fear of loss of or separation from the mother or mother-image, and the "lost cry" or "stifled cry" are constantly mentioned. Pozner[198] observed that a few brief interviews, analytically directed, were sufficient for the psychotherapy of asthma in two instances. It is doubted that such an approach will often be effective.

In eight asthmatic subjects, Funkenstein[94] found that the intramuscular injection of Mecholyl, contrary to his expectations, precipitated little or no asthma during real-life stress inducing situations; at other times, in the same subjects, severe attacks ensued. On the basis of simultaneous cardiovascular studies, he attributed this difference to the excessive secretion of an epinephrine-like or nor-epinephrine-like substance during psycho-

logic stress. The nature and significance of the psychologic stress apparently also help to determine the response.

For the purpose of prognosis, Berle and his colleagues[26] analyzed various data relating to the social status, past history, family and interpersonal relationships, past performance, personality structure, and attitude toward the illness in patients with stress diseases. After preliminary screening of 852 items, some thirty-seven were retained as informative in prognosticating the course of the disease. When the scale was applied to a group of sixty-seven asthmatics, there was considerable correlation between the "scores" made and the patient's subsequent clinical condition.

The psychodynamic pharmacology of the treatment of asthma was interestingly discussed by Abramson.[2] He pointed out that the reaction to and tolerance of various anti-asthmatic drugs may depend on the general psychologic type of the patient, and that a drug may intensify the symptoms because of the patient's mental state. Only a few examples can be given. The anxious asthmatic patient usually does well on sedatives, the depressed on amphetamine, and the grieving on minimal use of sedatives and sympathomimetic amines along with breathing exercises. The adrenergic amines should be used with caution in the hostile asthmatic, but barbiturates are tolerated in fairly large dosage. The euphoroid and phobic asthmatic patients require psychotherapy. The physician should utilize the action of drugs in an explicit relationship to the immediate, dominant emotional state of the patient.

EXPERIMENTAL ASTHMA AND INDUCED ATTACKS

In the September-October, 1951, issue of the ANNALS, Ratner[208] presented a critical analysis of the literature concerning experimental asthma. Since that time, the question of the induction of asthmatic attacks in man by the inhalation of aerosols of allergenic extracts has been studied by Herxheimer[118,119,120,121,122,123] of London; Lowell and Schiller[161,225] and Herschfus[117] of Boston, Arner[7,8] and Colldahl[56] of Sweden, Feinberg[83,246] of Chicago and others. Other techniques of producing asthma-like episodes under controlled conditions include the administration of histamine or acetylcholine by aerosol or injection, as employed by many of the same investigators, as well as by Sonne and Georg[243] and others. Such induced attacks fulfill a number of purposes: study of the mechanism, mechanics, functional derangements and characteristics of asthma; objective diagnosis in relation to specific allergens; determination of the degree of bronchial hypersensitivity; objective evaluation of the prophylactic and therapeutic effectiveness of anti-asthmatic and antispasmodic therapy; and attempts at bronchial hyposensitization. Most investigators, excluding Arner[7,8] and Feinberg,[83,246] employ some modification of a closed spirometer circuit, so planned that an asthmogenic or therapeutic aerosol may be delivered to the subject. Most include continuous recording of the respiration, and estimate the asthmatic situation by means of vital capacity, maximum breathing capacity, or other pulmonary functional determinations.

Herxheimer[118] pointed out that the attacks induced by aerosol inhalation in asthmatics vary according to the nature of the causative agent: after histamine and acetyl-beta-methylcholine chloride, attacks developed suddenly and violently. Sensitivity to both substances was much greater than in normal individuals and there were marked individual variations. After pollen and dust antigen, asthma developed gradually, sometimes many hours after inhalation, and became increasingly severe. Attacks

induced by molds usually showed no latency or late effects and subsided spontaneously. Attacks could not be induced with mixed bacterial vaccine.[119] The bronchial reaction was considered a more reliable diagnostic technique than cutaneous testing,[121] with respect to pollens, house dust, animal danders, and molds. The late bronchial reactions were more likely to occur with dust than with pollens, and in two of these patients, negative skin tests with dust became positive after nine hours.[122] Massive aerosol doses of allergic substances caused bronchial hypersensitization while small doses caused hyposensitization. Systemic bronchial hyposensitization was attempted by gradually increasing the amount of inhaled allergen under continuous control of the bronchial reaction.[119,121,123] Although assessment of results is concededly difficult, 86 per cent of seventy-two cases so treated showed improvement, and 27 per cent had a five-fold or more increase in their bronchial tolerance and required no symptomatic therapy.[123] These results were felt to be comparable to or better than hyposensitization by injection. The method is admittedly far from ideal, and is applicable only to a small proportion of asthmatics, but certainly advances our understanding of the mechanisms involved in asthma. Monovalent asthmatics, especially those sensitive to pollens, appeared to do better than polyvalent cases. The suppression of induced attacks by aerosol of isopropylarterenol did not interfere with the progress of the bronchial hyposensitization.

Schiller and Lowell[225] emphasized the inhalation test as a diagnostic procedure, employing pollens, molds and dust. A reduction in vital capacity of 10 per cent or more and/or a slowing of the expiratory rate with or without signs of asthma was considered indicative of bronchial sensitivity to the substance inhaled. Of seventy-five cases, fifty-seven reacted to one or more allergens, chiefly dust and ragweed pollen. There were many more skin reactions in this group, and the pulmonary response could not be satisfactorily predicted on the basis of skin tests, although none occurred with skin-negative allergens. Correlation of the results of inhalation tests with the season in which the patients had exacerbation of their asthma revealed that the dust season is shorter than usually thought and can be confused with the ragweed season, at least in the New England area. Their improved closed system apparatus is described[161] and revealed a decreased tidal volume and increased functional residual capacity in induced attacks. In 169 provocative bronchial tests, with different allergens in varying dilutions, on forty-four asthmatics, Colldahl[56] obtained 43 per cent positive reactions. Of patients with positive intradermal tests to autogenous dust, 72 per cent reacted to bronchial testing; with pollens, 59 per cent. In 16 per cent of trials, bronchial reactions were produced with allergens which were negative on skin testing. The test is considered reliable by these authors and should take its place with history-taking and skin testing as a diagnostic method.

Feinberg et al[83] ran repeated determinations of bronchial sensitivity in a series of patients with ragweed hay fever and asthma, employing a nebulizer with hand bulb and ragweed pollen extracts of ascending concentrations. Nasal and conjunctival sensitivity was also titrated. Patients with more than one year of subcutaneous hyposensitization therapy showed a lesser degree of bronchial sensitivity than did untreated asthmatics. The quantitative degree of sensitivity in the shock tissues correlated with the history of clinical symptoms. The method is proposed to evaluate variations in hyposensitization techniques, the preparation and modification of allergens, the effect of various nonspecific factors and nonspecific ther-

apy, and the decision as to when to discontinue therapy. Application of this approach in cortisone treated pollinosis cases[246] revealed a decreased mucosal sensitivity before the season, but, surprisingly, a moderate to marked increase in bronchial sensitivity at maximal cortisone dosage during the season. This is probably the result of a cumulative effect of the pollen applied artificially and that encountered naturally during the season.

Studies by Arner et al[7] showed greater hypoxia in experimentally induced and spontaneous acute asthmatic attacks (these two types revealing no significant pathophysiologic differences) than in asthmatic exacerbations in patients with chronic bronchitis and profuse expectoration. In the last-named type, administration of theophylline or epinephrine had a much slower effect in restoring the oxygen saturation of the blood toward normal, and accordingly bronchiolar spasm is thought to be less prominent in this situation. By means of an oximeter, Arner[8] also followed the decreased oxygen tension in attacks provoked by aerosols of dust, pollen, animal hairs and gum arabic.

Noelpp,[182,183] in a series of elaborate experiments on experimental asthma in guinea pigs, included synchronous recording of air flow velocity and intrapleural pressures. The findings suggested that changes in the elasticity of the lung play an important part in causing asthmatic ventilatory insufficiency, rather than bronchial obstruction alone. Preliminary, unpublished investigations in man, based on blood pressure, venous pressure and intraesophageal pressure determinations and pneumotachograms, indicate identical findings in human asthmatic attacks. Harrisson[110] described a simple aerosol apparatus and chamber for the production of experimental asthma in guinea pigs. Bentolila and Rabasa[23] again remind us that asthma can occur spontaneously in the dog; the necropsy findings are included.

PULMONARY FUNCTION TESTS

Since the excellent review by Segal et al[236] several studies of pulmonary function in asthma have appeared. Beale, Fowler and Comroe[19] outlined the value and limitations of the available pulmonary function tests. Disappointingly, application of such tests in asthmatic patients in the symptom-free interval was inadequate to indicate definitely whether changes in function were due predominantly to airway obstruction or to emphysematous changes. In general, there were a decrease in vital capacity and maximum breathing capacity (out of proportion to the reduction in vital capacity), abnormality in intrapulmonary gas distribution, a decrease in inspiratory capacity, an increase in functional residual capacity and in residual volume, and slight hyperventilation. Since the values of the first three tests improved following administration of a bronchodilator drug in many patients, the abnormalities were reversible at least in part, and it was concluded that many patients have definite bronchospasm in the absence of clinical signs and symptoms. To maintain lung volumes and pulmonary function at normal values in the symptom-free interval, it follows that continued and persistent therapy may be necessary. Pulmonary function tests may possibly be used to identify those patients with abnormal lungs in the interval and to predict the reversibility of the changes under treatment.

In appraising the ventilatory function tests as regards their practical and diagnostic value in 182 asthmatic patients, Berke et al[25] concluded that adequate pulmonary function evaluation requires comprehensive testing

beyond the facilities of the doctor's office. However, valid but limited information about the relative degree of functional and structural changes in a given patient may be obtained. The maximum voluntary ventilatory capacity (maximum breathing capacity) reflects most closely the clinical condition of the asthmatic patient, while the vital capacity expressed as a function of time is superior to static measurements of vital capacity alone.

The findings of Herschfus, Bresnick and Segal[116] are in substantial agreement with those above. At a time of complete comfort in forty-two patients, the tests revealed slight impairment of vital capacity, marked decrease in maximum breathing capacity and maximum expiratory velocity, a high index of intrapulmonary mixing, an enlarged total lung capacity and a high residual volume to total lung capacity ratio. Treatment with intravenous aminophylline or bronchodilator aerosols resulted in significant improvement in maximum breathing capacity, maximum expiratory velocity and the index of intrapulmonary mixing; slight improvement of vital capacity and of residual volume to total lung capacity ratio; little improvement in inspiratory capacity to vital capacity ratio; and no decrease of total lung capacity.

Students of the subject are urged to read these last three articles in full for their valuable discussions of the techniques and limitations of functional tests, and the possible mechanisms involved in the pathologic physiology of asthma and the changes produced by treatment.

Sonne and Georg[243] reported on the effects of subcutaneous histamine in thirty asthmatics. Typically there was displacement of the resting respiratory level leading to increased total lung capacity. The minute ventilation was increased in most patients, but the respiratory rate showed no consistent changes. Graphic registration of the respiration and determination of the minute ventilation were found to be more valuable indices than the arterial oxygen saturation. Colldahl and Lundin[57] employed a continuously registering nitrogen meter to demonstrate the ventilatory inefficiency of the lung in both induced (provocation tests) and spontaneous asthmatic attacks. Its great advantage was that it required a minimum of patient co-operation. Determining lung volume by the helium dilution method and ventilatory efficiency by carbon monoxide uptake in asthmatic children, Bates[18] demonstrated that cases of asthma of long standing may, in the absence of "bronchospasm" (detectable râles or rhonchi), have no abnormality in these tests; that when râles were present all cases had inequality of mixing (impaired intrapulmonary gas distribution); and that significant abnormality of function as judged by vital capacity, mixing efficiency, and carbon monoxide uptake may be present in the absence of accepted signs of bronchospasm. Briscoe[35,36] also emphasized the significance of uneven ventilation rather than an increase in dead space or reduction in tidal air in asthma and emphysema.

In closing this section, Barden,[17] although acknowledging the importance of the physiologic approach to pulmonary disease, is worthy of direct quotation: "Even when detailed laboratory tests of quantitative pulmonary function are not available, careful physical examination and fluoroscopic and roentgenographic examination directed to a demonstration of functional capacity will yield important information of a qualitative nature regarding pulmonary physiology. And, it may be added, the detection of qualitative differences remains the art of medicine."

DIAGNOSIS

Koelsche[149] outlined the clinical characteristics of asthmatic dyspnea as part of a symposium on dyspnea. Mansmann[165] recently discussed all phases of the etiologic diagnosis of asthma, including evaluation of the infectious and psychologic factors. Alexander[3] covered the differentiation between nonallergic and allergic bronchial asthma, as well as the treatment of the former. Eyermann[82] repeated a useful warning that wheezing dyspnea due to primary organic pathologic conditions should not be called asthma.

Both Juhlin-Dannfelt[138] and Arner[7] reiterated pleas for the employment of exposure and provocation tests under ordinary environmental conditions, admittedly old techniques, but too much neglected. They can be used not only to determine the etiologic diagnosis when skin tests are noninformative, but also to detect "latent" allergy, and the results were found to be largely reproducible. They can be applied to the diagnosis of sensitivity to dust, animal danders, pollens, et cetera. The utilization of inhalation tests for diagnosis has been considered above.

The roentgenographic findings in 200 unselected asthmatics were studied by Royle.[216,217] In uncomplicated asthma, the chest film was normal. The commonest abnormality was emphysema (in 28 per cent of children and 46 per cent of adults). Increased hilar shadows occurred more often in the infectious than in the noninfectious type. Segmental collapse was present in eight cases, most commonly in the right middle lobe; only one had physical signs and all re-expanded rapidly. Active pulmonary tuberculosis was found in three cases. Films were taken in full inspiration and expiration in an attempt to distinguish between irreversible emphysema and the pulmonary distention due to the bronchiolar obstruction of asthma, but were difficult to interpret and there was a wide margin of error. Sinus radiographs surprisingly showed a larger proportion of abnormalities in children (62 per cent) than in adults (54 per cent). The difficulties of the roentgenologic diagnosis of emphysema are confirmed by Knott and Christie.[148] Even with anteroposterior and lateral films in both inspiration and expiration, about 10 per cent of cases will be missed, and a few normals will be wrongly considered as emphysema. Undifferentiable changes also often occur in late middle age in subjects without chronic hypertrophic emphysema.

Jiménez Díaz and his colleagues[128,129] of Madrid reported a new radiologic technique of value in the diagnosis of asthma and affording some information concerning pulmonary function. Two films, one in forced inspiration and the other in expiration, are superimposed and compared. Changes in the position of the diaphragm, ribs and clavicles are sketched in. In normal subjects the movement of the diaphragm exceeds that of the ribs and clavicles. In asthma, both with and without complications, various patterns can be noted. The extent of rigidity of the thoracic cage and the degree of obstructive emphysema and of diaphragmatic excursion can be determined. The method is also helpful in recognizing the presence of bronchial obstruction, emphysema, atelectasis, congestion and edema, and fibrosis. In commenting on this article, Benson[20] pointed out that the method is not really new, having been used as early as 1934, and is inferior to a single-film double-exposure technique, first described in 1931. Schutz[227] preferred "movement sketches" during fluoroscopic study of the diaphragmatic movements.

Bronchographic studies in asthmatics between attacks, after instilling

lipiodol via the endotracheal tube, were carried out by Martin.[170] The oil stagnated in the larger bronchial trunks, in contrast to the normal findings, and inspiratory inflow stopped at the level of branches of the fourth order. The lumina of segmental bronchi were much reduced. The bronchi were sometimes filiform in appearance, and terminated abruptly as if amputated. There was little change in the bronchial caliber between full expiration and inspiration. These changes did not correlate absolutely with asthma. In some patients asthma-like dyspnea was brought on by the procedure.

In an extensive and beautifully illustrated article, Dubois de Montreynaud[72] reported on the bronchoscopic findings, bronchial mucosal biopsy, eosinophiles in secretions and tissues, and autopsy findings in a series of asthmatics. In allergic asthma, whether due to proteins such as wheat or horse dander or nonprotein substances such as pontocaine, bronchoscopy revealed a reduction in the lumen, an edematous mucosa of the branch bronchi and no hypersecretion. There was also thickening of the spurs of the branch bronchi, especially of the middle lobe. The asthmatic dyspnea in such cases is attributable to the mucosal edema. In contrast, nonallergic asthma, in which nothing in the history or skin tests accounted for the disease, showed about the same reduction in the bronchial lumen, but the mucosa was often dark and congested, although not edematous; there was also marked hypersecretion, often requiring aspiration. It was concluded that bronchospasm plus hypersecretion was responsible for the dyspnea in nonallergic asthma. Histologic studies of mucosal biopsies and autopsy specimens confirmed the bronchoscopic observations. The same studies in guinea pigs pointed up an interesting parallel: in anaphylactic asthma as from egg white sensitivity, bronchial edema predominated; in pharmacodynamic asthmatic dyspnea due to aerosols of bronchoconstrictive agents, bronchospasm was demonstrated. The therapeutic implications are obvious.

DIFFERENTIAL DIAGNOSIS

The practicing allergist is only too well aware of the fact that a number of unrelated diseases can simulate the symptoms, and to a considerable extent, the signs of bronchial asthma. Derbes and Coppedge[67] discussed the problems of differential diagnosis, presenting illustrative cases of asthmatic bronchitis, cardiac asthma, emphysema, hyperventilation syndrome, pulmonary tuberculosis, carcinoma of the lung, thymoma and aortic aneurysm—most of which had been diagnosed as asthma at some point in their clinical course. The patient of Courbin and Pène,[60] although considered to have asthma, died of a pulmonary malignancy, while Green's[105] case had asthmatic wheezing for five years until it was ultimately found to be caused by a large papillomatous endotracheal tumor. Muhleisen[179] observed asthmatic symptoms lasting five days due to the pulmonary migration of the hookworm larva of *Ancylostoma braziliense*, the causative agent of larva migrans or creeping eruption. Filariform larvae were recovered from the sputum daily for twenty-four days. The report of Black et al[27] is of interest in that a foreign body, the shell of a pistachio nut, was retained in the respiratory tract of a nine-year-old girl for about fourteen months. During this time, wheezing was heard at each clinic visit, but anti-asthmatic therapy was, of course, unsuccessful. The shell was finally coughed up spontaneously, with the resultant clearing of all symptoms and signs. Brown[39] discussed the differential diagnosis

and the mechanisms of the cough in asthma and tuberculosis, as well as in other diseases.

Bradford[32] outlined the characteristics of "progressive bronchospastic disease resulting in emphysema of obstructive type," sometimes called "primary obstructive emphysema." While the clinical picture differs considerably from that of asthma, the condition is often misdiagnosed as intrinsic asthma. It is a common disease, occurring chiefly in males over fifty years of age, and rarely in females. Spasm of the smaller bronchi and bronchioles is the predominant clinical finding, with pulmonary emphysema as the final structural change. No râles are heard at any stage. Cardiac decompensation appears late in the course. Adequate pathologic studies have not been made, in part because of the prolonged course of the disease. The etiology is speculative, there being no proof of infection or hypersensitivity; it is hypothesized that some disturbance of the physiologic function of the nerve supply to the lungs may be involved. Tapia[250] described a similar syndrome under the title "subacute progressive idiopathic bronchiolar stenosis syndrome of unknown cause" but differing in the fatal termination.

Pulmonary fibrosis may be associated with asthma, asthmatic bronchitis and emphysema, according to Peabody et al.[194] Roentgenograms of the thorax show bilateral diffuse parenchymal infiltration, though not diagnostic. Pulmonary fibrosis is usually found to be associated with other disease states, such as lymphatic metastatic carcinoma, bronchiectasis, organized pneumonia, aplastic anemia, and so on. Only one instance was confirmed by necropsy to be "of indeterminate origin."

The differentiation of asthma and cardiac dyspnea is by no means always easy, and the differing opinions are well illustrated by four recent articles. Perlman[196] states that there are no infallible guides to differentiate between cardiac insufficiency and asthma as a cause of dyspnea, wheezing and coughing in elderly patients. Many of the symptoms are common to both conditions and the results of a therapeutic trial cannot be relied upon to establish the diagnosis. Aminophylline is likely to help both conditions. Although no single factor can be considered pathognomonic, certain symptoms and tests are more strongly indicative of one condition than of the other. Prolonged circulation time would seem to be the factor most strongly indicative of cardiac disease, and eosinophilia in blood and secretions, of asthma; yet often in obviously asthmatic patients eosinophilia is not present, and often in the presence of unquestionable paroxysmal left ventricular failure there is no significant lengthening of circulation time. Other indications may be found in the history, gross and microscopic findings in the sputum, and the presence or absence of fine basal râles. Two cases are described in detail. It is evident that in mild congestive heart failure an intrinsic bronchial disorder may become prominent, while a patient with a long history of bronchial asthma is just as likely to develop cardiovascular disease as the non-asthmatic. Careful evaluation of all factors, while not always establishing an unequivocal diagnosis, will provide a basis for judicious treatment. Schuman and Simmons[226] determined the circulation times and response to intravenous aminophylline in thirty cases of bronchial asthma, thirty-five of cardiac asthma, and ten considered to have both. Arm-to-lung (ether) and arm-to-tongue (Decholin) circulation times were on the whole normal in bronchial asthma and prolonged in cardiac asthma. The cardiac group, except for four patients, was generally unimproved by aminophylline. The wheez-

ing of cardiac asthma is thought to result from vascular dilatation and pressure on the bronchi; the possibility of bronchospasm is not admitted.

Gelfand and Widlitz,[100] while granting that circulation times are often valuable, especially when both diseases coexist, point out that they may occasionally be normal in early left ventricular failure and frequently cannot be done when most needed. They agree with the earlier observation of Plotz that bronchospasm accompanies the pulmonary congestion of left ventricular failure. They treated six patients, all more than fifty years old, with long-standing allergic bronchial asthma who suddenly failed to respond to their usual antiallergic therapy. Although all had evidence of hypertensive and/or arteriosclerotic heart disease, as well as pulmonary fibrosis and emphysema, none were in frank congestive failure. Injections of mercuhydrin resulted in marked clearing of the pulmonary signs and dramatic relief of dyspnea in several hours; maintenance dosage of mercuhydrin was followed by an improvement of the asthmatic state. As controls, twenty patients with uncomplicated asthma under forty years of age were given 2 cc doses of mercuhydrin subcutaneously during paroxysms and no benefit was noted. It was concluded that the administration of mercuhydrin may be useful in the recognition of a cardiac factor as a complication of bronchial asthma. Lombardo and Harrison[158] attribute the difficult expiration of cardiac dyspnea to congestion and edema of the bronchial mucosa, compression of the bronchioles by engorged capillaries, and fluid in the bronchioles. They found aminophylline frequently beneficial, probably by causing bronchodilatation and increasing coronary blood flow. Morphine, while relieving dyspnea and anxiety, may prove fatal to cardiac patients with pulmonary emphysema.

TREATMENT: GENERAL CONSIDERATIONS

An interesting editorial[78] reviewed some of the bizarre and outmoded therapeutic techniques of the decade 1932 to 1942. One cannot help but wonder if a reprise in 1963 will make our current efforts seem as outlandish and futile.

The general management of asthma has been described recently by Unger and Unger,[255,258] including an excellent section on preventive treatment in children of allergic parents, by Fulton,[93] and Koelsche et al;[150] of an asthmatic paroxysm, with special emphasis on the physiologic and electrolyte imbalances, by Brown;[38] and of status asthmaticus by Eisenstadt,[79] Segal and Herschfus,[234] and Kaufmann.[142] In a symposium, Wescott,[280] L. N. Gay,[97] Chobot,[49] and Bruger[41] discussed the treatment of asthma due to external inhaled factors and intrinsic factors, symptomatic therapy, and the pharmacology of the relevant drugs, respectively. There was no unanimity of opinion regarding such controversial issues as the use of stock and/or autogenous vaccines, radium therapy to the nasopharynx, and the precise place of ACTH and cortisone.

Heckscher[111] seriously questioned whether it is desirable to employ drugs to terminate status asthmaticus as promptly as possible. He objected to the use of aspirin, epinephrine, ephedrine, theophylline, atropine, sedatives, and even ACTH as transitory and palliative. Potassium iodide acts as a little longer, but not much. All drug therapy causes disappointment. He aimed at long-lasting relief by fostering a change in behavior on the part of patients. by calming and relaxing the tensions set up by anxiety and muscle strain, by insisting on a lateral decubitus on a hard bed with the head low, and by encouraging more effective respiratory movements.

All this was an introduction to the subsequent employment of posture-correcting remedial exercises previously described by the author. In 654 hospitalized cases of status asthmaticus, this technique along with nikethamide and caffeine every two or three hours in drop form or by injection if necessary, gave some relief of asthma, but not dramatically so—this being considered an advantage. Iodides, sulfonamides, and antibiotics were used in some cases, but epinephrine, ephedrine and morphine hardly at all. Fatalities in ten patients reported in some detail appeared to depend on the administration of epinephrine and in two instances, of morphine before admission to the hospital; or on the co-existence of heart disease or bronchiectasis with pneumonia. In the absence of such factors, status did not entail an immediate risk of death, even when persisting for some time. Many patients remained in status for three to fifteen days, and some for much longer. No exact conclusions were drawn, but "medical gymnastics" were favored over currently employed treatment methods. This reviewer feels, however, that few patients presently treated suffer nearly so long. It is granted that there is much overtreatment of status. The importance of a calm demeanor of the attending physician has long been recognized. And it is seriously doubted that epinephrine, if used intelligently, is as dangerous as Heckscher implies.

Sterling, Fishman and Sherman[247] hold that refractory asthma results from acute or chronic infection or indirectly from disturbed digestion and a poorly functioning gastrointestinal tract. In their patients, abdominal distention is often followed by asthma. They employed various measures to build up the patient's general well being, such as injections of liver extract and vitamin B complex, and pancreatin and other measures to correct deficient digestion.

F. S. Gay[96] of Biloxi, Mississippi, outlined his method of therapy for the first time. Aside from medication, a sympathetic approach to the patient's every-day problems, reassurance by and a helpful attitude of the physician, and the avoidance of too many restrictions is emphasized. The most important phase of treatment lies in "patient control." This is fostered by such measures as the appointment system, daily visits for about a week, indoctrination, and periodic progress reports after the patient leaves Biloxi. Self- and group-therapy attendant on meeting other sufferers is admittedly important. For the acute attack, all standard procedures are employed, but sparingly and rarely for more than four days; the status patient is said to be overmedicated and overstimulated, resulting in a vicious cycle. The basic medication for "permanent relief" consists of small doses of Fowler's solution (rarely more than 10 minims per day), potassium iodide (seldom over 15 grains per day) and phenobarbital (usually less than 3 to 4 grains per day) in an aqueous solution or suspension, with a few minums per dose of tincture of digitalis for "catalytic effect." Coloring and saccharine are usually added, or a syrup used at times. The dosages depend on the patient's general health, age, weight, nervous tension, and history of drug sensitivity. The dosage frequency is gradually reduced, generally by two-thirds in a period of six months, but maintained for over two years in the amounts necessary, with wide variations. Calcium preparations are beneficial, but are avoided in cardiac, arteriosclerotic and elderly patients. Daily intestinal evacuation is important, and accomplished by bile salt preparations or laxatives. For nasal obstruction, amphetamine in light liquid petrolatum is employed. Antihistamines are used only as a relief agent, being best in children and cases of recent origin. Acute respiratory and chronic bronchial infec-

tions are promptly treated with antibiotics, chloromycetin being preferred. Nebulizers, epinephrine, aminophylline and ephedrine are avoided except in real emergencies. Skin tests and desensitization are not employed, a "general desensitization" being thought to result from the medication. The procedures are not curative but give favorable results in the great majority, and there have been no known deaths from medication. The occasional arsenical and iodine reactions have been corrected without mishap; prolonged administration, with reasonable safeguards, is not harmful. Results have not been good in complicated cases with bronchiectasis, emphysema, cardiac decompensation, hepatic cirrhosis and chronic nephritis. "There is no secret formula employed unless it be that of experience . . . we cannot condemn too strongly the tendency to treat all patients with an identical prescription." Gay states that his patients suffer less pathologic change than from any other medication offered, and that he will revise his therapy when modern medical science determines the etiology of asthma.

Three recent reports attest to the fact that Fowler's (potassium arsenite) solution in the "Gay" mixture is far from harmless. Pascher and Wolf[193] reported two cases of cutaneous manifestations with hyperpigmentation (melanosis), one also having arsenical keratoses and keratoderma. Silver and Wainman[240] and Pelner and Waldman[195] described instances of chronic arsenic poisoning with melanosis, keratosis, gastroenteritis, hepatitis and neuritis. All four patients had taken the "Gay asthma mixture" for periods of fifteen to twenty-eight months.

TREATMENT: CORTICOTROPIN AND CORTISONE

Since the excellent reviews of Segal and Herschfus,[233] Brown,[40] and Evans and Rackemann,[81] reports on the treatment of asthma with ACTH and cortisone have continued to appear in large numbers. Comparison of methods and results is virtually impossible because of differences in case selection, dosage schedules, length of treatment, criteria for evaluating results, and the simultaneous or alternating use of both preparations in some instances. Appraisal of the reports leaves one confused as to the precise place such therapy should occupy in the best interests of the patients. While the immediate results have, on the whole, been striking, disappointment is frequently expressed at the unpredictability of and the often relatively brief duration of remissions. These agents may be life-saving in patients in status asthmaticus who do not respond to other measures. They probably have therapeutic value in other patients whose therapy is unsatisfactory, especially in intrinsic asthma without too advanced pulmonary emphysema. Cor pulmonale and emphysema seem to be present in many of the cases considered as therapeutic failures. There is general agreement that the decrease in the number of circulating eosinophiles does not always correlate with clinical improvement, and is not a reliable guide to dosage. Side-effects act as a limiting factor in some cases, but severe untoward effects are statistically infrequent with the dosage schedules commonly employed. The masking and adverse effects of these preparations on infections of the lungs, paranasal sinuses, and other organs have been amply discussed. Corticotropin and probably also cortisone may rarely produce anaphylactic reactions.

The literature indicates growing interest in finding a maintenance program in order to obtain more prolonged remissions and in the intravenous use of ACTH in the interests of a more rapid response and of economy.

Lowell et al[160] attempted prolonged treatment in nineteen asthmatics, giving cortisone continuously or intermittently for one year or more. Daily maintenance dosage ranged from 50 to 150 mg, varied in accordance with the patients' needs. All but two of the patients maintained a satisfactory state of health, but there was no evidence that the underlying disease was materially influenced. The principal side effects were weight gain and hypertension, the latter perhaps coincidental. Recurrent respiratory infections were sometimes difficult to recognize, manifested chiefly as an exacerbation of the asthma without striking symptoms, fever, or physical findings. They were best treated with antibiotics and usually required a temporary increase in the dosage of cortisone. Peptic ulcers and reactivation of healed pulmonary tuberculosis (two cases) did not occur.

Ambulatory treatment of nine cases after satisfactory response in the hospital was tried by Baldwin and de Gara.[16] Cortisone in daily doses of 75 to 100 mg and ACTH in amounts of 40 to 80 mg were given for periods of twenty-six to 210 days. Only three patients were able to discontinue the use of either drug without relapse. No serious side effects were experienced, all patients being kept under careful medical supervision. In an intensive study of six cases, Burrage et al[44] attempted to determine the minimal or optimal maintenance dose of cortisone. Each patient was found to have an optimal maintenance level, usually between 62.5 and 75 mg per day, but varying from time to time in the same individual. All gained weight without gross edema, but there were no serious undesirable effects. Harris[109] tried various dosage techniques in twenty asthmatics. After one week of therapy, with initial daily doses of 200 mg or more of cortisone, relapse occurred in one to thirty days, usually in less than eight. Retreatment was effective, but the results were less impressive. Intermittent ACTH therapy during the tapering off of cortisone did not delay the relapse. While low dosage maintenance therapy, usually at the level of 50 mg of cortisone per day, deferred the relapse for twelve to thirty-five days, all cases eventually relapsed. The group given relatively high dosage, over 150 mg a day, had no relapses, in some up to sixty days after the discontinuance of therapy.

Mitchell and Cameron[177] found oral administration of cortisone as effective as intramuscular. In most cases, 200 mg. were given the first day, and then 100 mg daily for several days. Relapses usually followed discontinuance of therapy in from one week to three months. One patient was maintained on cortisone for ten months without ill effect. One was relieved by corticotropin after failing to respond to cortisone. In thirty cases of severe perennial asthma, Blumenthal[29] observed good responses in twenty-two and fair in eight during the initial course of oral or parental cortisone. Five patients had prolonged remissions, but twenty-five had to be maintained on oral doses varying from 25 to 75 mg daily. During exacerbations larger doses were required. No serious deleterious effects were noted.

It is stated or implied by the investigators attempting prolonged therapy that it is intended, barring adverse side effects, to maintain treatment indefinitely.

The generally prompt benefit of ACTH therapy of status asthmaticus has received further confirmation in recent reports. Johnsson and Skanse,[135] employed daily doses of 20 to 40 mg for at least three days and observed only one failure in seven patients; this case responded favorably to cortisone. Nattrass and Latner[181] administered 25 mg of ACTH every six

hours to thirteen status cases; the immediate results of short-term therapy were impressive, but there were no prolonged remissions. Valéry-Radot et al[260] noted favorable responses in twelve to twenty-four hours in seventeen instances; in six asthma recurred within a period of two months, but four had remissions lasting two to eight months. Two others died in severe asthma on the twenty-seventh and thirty-fourth day of therapy.

Intravenous corticotropin has given excellent results in continuous or intermittent courses, according to Segal and Herschfus,[235] Hedström,[113] Arbesman,[5] Lockey,[157] and Hampton.[107] Segal[235] used 30 mg daily in 3 liters of 5 per cent glucose with added aminophylline, for a total dosage of 10 to 210 mg in one to nine days. Seven of their ten patients experienced excellent remissions lasting up to six weeks, and the others partial remissions. Hedström[113] gave 2 to 3 mg diluted in 10 cc of normal saline three times a day. All sixteen patients became symptom free in three to six days, but all relapsed within five weeks after discontinuing therapy. Arbesman et al[5] employed an initial dose of 20 mg daily taking eight to twelve hours. The daily dose was gradually reduced over a period of six to fourteen days, for a total dosage of 75 to 220 mg. Of thirty-three such courses, twenty-seven produced symptomatic relief within twenty-four to forty-eight hours, and twenty-two were followed by freedom of symptoms for three to four weeks. They attempted to prolong the remissions by the administration of oral cortisone and found marked variations in the minimal dosage required, with favorable results in most instances. Lockey et al[157] employed 10 to 80 mg per liter of fluid each twelve hours, in continuous therapy, although favoring the smaller dosages after increasing experience. Hampton[107] found continuous (using 10 or 12.5 mg per liter) to be superior to intermittent therapy. Nearly as effective was a program of a single intravenous infusion during the day, supplemented by an intramuscular injection of ACTH at midnight.

All these investigators were impressed with the greater efficiency, more rapid relief of symptoms and physical signs, and the greater economy of intravenous administration in comparison to the intramuscular. The present reviewer is in complete agreement on the basis of his own experience, but prefers to switch to intramuscular therapy after one to three days for reasons of patient comfort and simplified nursing care.

The difficulties of surgery in the uncontrolled asthmatic is widely appreciated. Corticotropin and cortisone therapy preoperatively greatly simplifies this problem, according to Prickman et al[200] and Cooke.[58] No interference with wound healing or other complications were noted.

Intrabronchial administration of cortisone is highly effective according to several preliminary reports. Gelfand,[99] Doerner et al,[70] and Marshall[168] employed an aerosol method, while London and Alexander[159] instilled the drug via an intratracheal cannula or by means of a bronchoscope. Further study of these techniques is justified, but the present reviewer, who has tried aerosols of both cortisone and hydrocortisone (Compound F) in a number of patients, is very dubious that it has any clinical advantage over customary methods.

Raben et al[204] pointed out that it is possible to prepare a highly purified corticotropin which appears to be about 150 times as effective clinically as the standard corticotropin. Further clinical evaluation is required to determine the effective dosage.

Deaths during ACTH and cortisone therapy were reported by van Ufford[267] and Zoss and Zodikoff[289] though in neither instance could the

fatality be attributed directly to the therapy. Driscoll and Sass[71] observed an immediate anaphylactic reaction following an intramuscular injection of ACTH. Hyposensitization was apparently successful.

TREATMENT: NITROGEN MUSTARD

Since the physiologic effects of nitrogen mustard are somewhat similar to those of corticotropin, including eosinopenia, increased urinary 17-ketosteroids, adrenal hyperplasia, and antimitotic and lympholytic properties, Jiménez Díaz and his co-workers[127,130,131,132] gave it intravenously in intractable asthma and prolonged status asthmaticus. Of seventeen patients, eleven had complete relief and three were improved. Some of the remissions lasted many months. A number of reports from Italy, Spain, Argentina and elsewhere confirmed the results. Ovalle et al[191] of Chile had no success in three cases and were troubled by toxic effects.

Salomon[222] of New York treated six cases with 5 to 6 mg on two successive days. All responded well but one; the failure was subsequently dramatically relieved by cortisone. Triethylene melamine, a compound related to nitrogen mustard, was totally ineffective. Waldbott[271] administered 0.1 mg per kilogram of body weight to twenty-one patients with severe intractable allergic asthma. All but two had considerable relief for periods of one to seven weeks, with cessation of asthma after the second or third injection. Most relapsed within a few weeks. Side effects were fairly common. Nitrogen mustard is contraindicated in pregnancy and in patients with a tendency to hemorrhagic diathesis or leukopenia. It may prove useful in asthmatics with hypertension diabetes or concurrent infections where ACTH is contraindicated. The present writer had no success with nitrogen mustard in two cases. Its ultimate place in therapy remains to be proved.

TREATMENT: IRRADIATION

Mueller and Flake[178] confirmed the benefits of roentgen irradiation and radium application to the nasopharynx in forty-one asthmatic children whose disease was clearly associated with respiratory infection. Complete relief or marked improvement was noted in 68 per cent, and fair results in 12 per cent. The two techniques appeared to be equally effective, and untoward effects insignificant. The results were largely dependent on a reduction in the frequency and severity of subsequent respiratory infections. Increased benefit from hyposensitization was noted in some cases following irradiation. Nine cases were given a second course of treatment after periods of six to twenty-four months.

Vannfält[261] found roentgen therapy to the chest (three treatments of 200 to 250 r applied to four fields with copper or tin filtration) to be of some value in asthma, as determined by follow-up studies of sixty-eight patients. More than half preferred it to medicinal treatment. Seven cases had remissions for more than one year.

TREATMENT: SURGERY

Attempts to influence asthma surgically continue. Hansen[108] operated on thirty-seven patients with intractable, so-called non-allergic asthma, who had failed to respond to previous therapy. Three patients died postoperatively. Eighteen patients treated with high thoracic sympathectomy showed good results in seven cases, and twelve treated with vagotomy,

usually bilateral, in five cases, on follow-up after one to eight years. Eight of these cases were observed for over three years. Poor general condition and slight or moderate cor pulmonale were not regarded as contraindications. Clarke[52] performed bilateral resections of the vagus in six cases of intractable asthma. The results were on the whole disappointing, but further trial of this approach was deemed justified. Pulmonary denervation was carried out in twelve patients by Boone.[30] Seven were free of symptoms during relatively brief periods of postoperative observation.

Weille and Richards[278] discussed the influence of paranasal sinus surgery on asthma on the basis of 197 patients followed for six months to twenty-six years. Of the entire group, 52 per cent were apparently benefited, 48 per cent were not, and 18 per cent were worse as regards their asthma. The longer the period of follow-up, the better the overall results seemed. Recurrent polyposis and failure to control vasomotor rhinitis and nasal obstruction accounted for many of the failures. On the whole, relatively conservative surgical measures seemed adequate and gave slightly better results in asthma than did the more radical measures. It was concluded that the majority of asthmatics submitted to sinus surgery will not, in the end, grow worse, and that essential "cure" by such operations cannot be achieved. On the basis of the evidence presented the reader is tempted to render a Scotch verdict of "not proved" as regards the value of sinus surgery in asthma.

Clein[53] found that in some children allergy may be a contraindication to tonsillectomy and adenoidectomy. The effects may be harmful rather than beneficial. Asthma has been precipitated by the operation, especially when performed during the pollen season, in children with seasonal hay fever. It is recommended that the allergic state be treated first and the indications for tonsillectomy then considered on the same basis as in the nonallergic. Postoperative lymphoid regrowth is much more likely to occur in allergic children. In a review of 1,317 cases of asthma, Hedström[112] found that fifty-two had undergone tonsillectomy. Of these, four had had an exacerbation of asthma after operation, eight were improved, and forty showed no change.

TREATMENT: ANTIBIOTICS AND VACCINES

An Editorial[77] in the ANNALS discussed the desirability of controlling the bacterial invasion which so often seems to be responsible for the activation or intractability of asthma. But no final decision can as yet be reached as to the best means of achieving this desirable end. Bubert[42] favored procaine penicillin in doses of 1,200,000 units every three or four days for several doses. Of sixty-eight asthmatic episodes, 69 per cent were so controlled. Frouchtman[91] reported a rapid response to aureomycin in three patients with long-standing infectious asthma resistant to penicillin. Rosen [213,214] found terramycin valuable in twenty patients whose asthmatic attacks were preceded or accompanied by an upper respiratory infection. The initial dose was 500 mg at the onset of wheezing, followed by 250 mg three times a day for ten doses, each dose being taken with milk. Thirteen patients were relieved within forty-eight hours, a few within twenty-four, although most had noted that previous attacks would last four to seven days. In ten cases of intractable asthma associated with bronchiolar infection, Segal et al[232] were impressed with the effectiveness of combined terramycin and bronchodilator aerosol and the absence of allergic reactions.

The increasing use of penicillin and penethamate hydriodide (neo-penil)

justify a word of warning regarding possible severe anaphylactoid and even fatal reactions.[172,209] One of Mayer's[172] patients had asthmatic manifestations during penicillin anaphylaxis. Since we are here concerned with an allergic population, caution may be reasonably enjoined. Careful questioning regarding previous reactions and skin testing in any doubtful case, although not always reliable, are wise precautionary measures.

In answer to a query,[203] acceptable advice to prevent the activation of asthma following "colds" includes small doses of ephedrine and iodides, a course of treatment with a vaccine made from the usual bacterial flora of the respiratory tract to minimize the bacterial inflammation in the bronchi, and when an allergic etiology is present, the elimination of the inhalant or food allergens to deprive the colds of their asthma-producing tendencies. Bergquist[24] found that therapy with autogenous vaccine was markedly beneficial in 341 cases followed for two to five years. Good results were reported in 80 per cent of cases of intrinsic asthma and in 72 per cent of extrinsic. The latter type were given specific desensitization before the autogenous vaccine. The cultures yielded Staphylococcus aureus and albus predominantly. The dosage of vaccine was 1 million organisms, increased weekly to a maximum of 200 million, and then held at half this dose each month for one year. Children were given from one-tenth to one-half as much. Baird[12] preferred a stock bacterial antigen plus antibody, called "serobacterin" or "sensitized vaccine," in larger doses than usually recommended. He found that an initial injection representing 1,400 million killed bacteria of seven varieties, followed by increasing dosage up to 15,000 to 20,000 million organisms gave some relief to nearly all his cases of asthma.

The technique of Whiteman[281] outlined in a small monograph, is not likely to be accepted. Emphasizing the importance of sinus infection and "nasal catarrh" in all cases of asthma, he recommends bed rest for several weeks, followed by bilateral antrostomy, and then repeated antral lavages with normal saline. Inhalation of menthol and eucalyptus for several hours daily and continued for four to six weeks follows. At the first signs of a subsequent "cold," bed rest and the inhalations are resumed. The results are "almost invariably successful!"

TREATMENT: PYROGENIC AGENTS

Piromen (formerly Pyromen) was found to be a definite aid in fifty cases of perenial asthma by Wittich[287] especially when combined with specific allergic therapy. Beneficial results were slower than those following ACTH or cortisone therapy, but the relatively few ill effects were thought to warrant its further trial. Subfebrile intravenous doses ranging from 0.5 to 15.0 micrograms were recommended. Piromen is a bacterial polysaccharide derived from a *Pseudomonas* organism, which when administered parenterally produces a marked leukocytosis and evidence of activation of the reticulo-endothelial system. According to Samter and Kofoed,[223] subcutaneous injections of piromen in subfebrile dosage in thirteen cases of asthma of moderate severity failed to indicate a clinical effectiveness superior to a placebo. The reviewer's experience in a small group of asthmatics was also very disappointing. Walton and Elliott[275] reported the necropsy findings in a patient dying unexpectedly about one and one-half hours after the seventh intravenous injection of piromen. It was not possible to say whether the use of piromen was causally related to the fatality.

Pyrifer, a febrogenic preparation from killed bacteria of the coli group, has long been used abroad. Kremer[152] found such fever therapy beneficial in intrinsic asthma in which bronchitis was the sole or dominant etiologic factor, with remissions lasting for weeks, months or years. When both extrinsic and intrinsic factors are involved, the former should be treated first. In purely extrinsic cases, the value of pyrifer was limited, but helpful in some instances of prolonged and resistant status asthmaticus.

TREATMENT: PHARMACOTHERAPY

Some of the recent evidence regarding the effectiveness of antiasthmatic medication has been cited above, in the sections on induced attacks and pulmonary function testing. Berke et al[25] compared the effect of various medications on the ventilation function tests of asthmatics. Epinephrine gave the most consistent and significant changes. The results with intravenous aminophylline were puzzling: despite marked clinical improvement, the function tests showed little, if any change. Antihistamine drugs were effective in seasonal, but ineffective in chronic perennial asthma. Placebos for oral medication, especially if resembling an effective ephedrine-containing compound in shape and color, sometimes afforded subjective relief, but without improving the measured ventilatory capacity.

Herschfus and his co-workers[117] summarized their evaluation of a large number of therapeutic substances on asthmatic paroxysms induced by intravenous and aerosol administration of histamine and methacholine and by aerosols of potent allergens as measured by vital capacity determinations. The results varied depending on the nature and route of administration of the asthmogenic and therapeutic substances. Only intravenous aminophylline gave a high degree of protection against aerosols of house dust. Intravenous aminophylline, atropine, and benadryl, and isuprel aerosol were generally effective against attacks induced by inhalant aerosols such as feathers and dog and horse danders. Solid aerosols ("dusts") of aminophylline, diphenhydramine (Benadryl), and isopropylarterenol (Isuprel) seemed to offer no particular advantages over liquid aerosols, and presented some disadvantages. The results of this bio-assay method agree in a general way with clinical results. The effects of a purely anticholinergic drug such as atropine emphasizes the importance of the parasympathetic nervous system in the mechanism of asthma; however, atropine, scopolamine and Bellafoline have a very limited therapeutic rôle because of their undesirable drying action on the bronchial mucosa. Drugs with high antihistaminic property only are clinically more effective than those with only anticholinergic properties. The ideal antiasthmatic drug would be one having both effects.

"Multi-purpose" combinations are widely employed. Ratner[207] recommended Collergy tablets, containing phenobarbital, theobromine, ephedrine sulfate, atropine sulfate, acetylsalicylic acid, and aluminum hydroxide. Fond[85] confirmed the efficacy of Nethaphyl, consisting of nethamine hydrochloride, butaphyllamine, and phenobarbital. Silbert[239] arrived by stages at a mixture of ephedrine sulfate, potassium iodide, and syrup of phenergan in belladenal elixir.

Antihistaminic Drugs.—It is safe to say that most observers do not favor antihistamines in the treatment of most cases of asthma. However, Wolfe[288] reported success with pyribenzamine and benadryl. Shure et al[238] employed Tri-Histin, consisting of three different antihistamines, and had

good to excellent results in 22.8 per cent of cases—about twice the figure obtained with a placebo. Abroad, prompt termination of paroxysms in a large proportion of instances after inhalation of antihistamine aerosols was reported by Gonzalez[103] and Benstz and Holldach.[21] Boyd[31] found chlorprophenhydramine maleate (chlortrimeton) administered orally or subcutaneously had no expectorant effect in aminals, and concluded that antihistamines are of no value in the routine treatment of cough.

Histamine.—Jonez[136] advocated the deep intramuscular injection of histamine in a repository menstrum of peanut oil and oxycholesterol derivatives (histapon) in cases of asthma when hyposensitization failed or the causative agents could not be discovered. This was carried out by self-administration by the patient in increasing amounts; individualization of the dosage was guided by the symptoms and reactions.

Procaine.—According to Markow, Bloom and Kleinman,[167] the oral administration of procaine hydrochloride in doses of 300 mg was of little value in the treatment of asthma when compared to an ephedrine-theophylline combination. The high incidence of side reactions was not materially controlled by adding ascorbic acid. Stearns et al[245] reported that of four asthmatics with cardiac arrythmias treated with procaine amide (pronestyl), two suffered profound hypotension associated with convulsive movements and in two, acute asthmatic attacks developed.

Khellin.—Sharply contradictory opinions have recently been expressed regarding the value of khellin or visammin, a crystalline derivative of the plant *Ammi visnaga*. Derbes and his co-workers[69] relieved about 60 per cent of acute attacks with 100 mg doses, there being no appreciable difference between oral and intramuscular administration. Advantages were its prolonged action and minimal effect on blood pressure. According to Braun and Eilender,[38] khellin was very effective as an aerosol in amounts of 7 mg inhaled in five minutes. Prompt and uniform improvement followed in all ten paroxysms so treated and the vital capacity increased.

Pulmonary circulation and cardiac output studies by means of cardiac catheterization in patients given 200 mg of khellin intramuscularly convinced Cash and Zimmerman[47] that the therapeutic usefulness of this drug in cor pulmonale and asthma is doubtful. Snider et al[242] employed vital and maximum breathing capacity determinations to compare the effect of 120 mg of khellin orally per day with that of a placebo. There was no reduction in the frequency of acute attacks or the number of injections of epinephrine required during the period of therapy. No patient showed a significant rise of vital capacity and only three out of eight, a minimal increase in maximum breathing capacity. Another group were given 300 mg of khellin intramuscularly during acute paroxysms. All reported partial relief, but maximum breathing capacities were not significantly improved, although subsequent administration of aminophylline intravenously or epinephrine subcutaneously increased the figures greatly. The present reviewer has been equally disappointed in the clinical effectiveness of oral khellin.

Aminophylline.—The essential safety of intravenous aminophylline, in the absence of hypersensitivity, is indicated by a patient with asthma who received over 1,000 injections in four years, sometimes three or four times

daily.[202]. Whitfield et al[282] concluded, on the basis of detailed ventilatory function studies, that oral aminophylline has no place in the treatment of emphysema in the absence of bronchospasm. Waxler and Moy[277] demonstrated marked individual variations in the absorption of aminophylline from the rectum, as shown by determinations of the theophylline blood levels. Most cases, however, had significant values at the end of three hours. It appears that the suppositories may be more effective in those with good rectal absorption.

Adrenergic Agents.—Attempts to improve on the clinical effectiveness, ease of administration, duration of action, and incidence of side-effects of the accepted adrenergic agents continue. A long-acting epinephrine in a 1:200 suspension in an aqueous vehicle containing glycerine and thioglycolate (Sus-Phrine) and administered by subcutaneous injection was successfully used by Unger and Unger.[256] and Naterman.[180] In comparison with epinephrine in oil or gelatine, advantages include a more rapid onset and greater duration of effect, simpler technique of injection, and easier self-injection by the patient. Ouer[190] was able to prolong absorption by incorporating epinephrine in solutions of algin, extracted from giant kelp, and called "Algin-ephrin."

Mitchell[175] added two cases to the few previously reported, of local sensitivity to epinephrine of animal origin. Following the inflammatory reactions, depressed scars appeared. The reaction apparently is due to a local fixed tissue sensitivity, occurring only in areas where many injections have been previously given. Synthetic epinephrine and epinephrine derivatives did not produce this inflammation.

A "blind" comparison of several solutions of epinephrine and related substances for aerosol inhalation for the relief of paroxysms by Lewis-Fanning and Parr[155] revealed no superiority of special commercial preparations to the official epinephrine solution. Da Costa[64] warns that the indiscriminate use of the epinephrine nebulizer is harmful, in injuring the ciliated epithelium and causing circulatory disturbances.

Orthoxine, a sympathomimetic amine chemically related to ephedrine, was not significantly superior to a placebo in affording symptomatic relief in controlled groups of asthmatics, according to Ogden and Cullick.[186] In adult office patients, a large proportion had definite benefit from oral doses of 50 to 200 mg taken several times daily or as required; side-effects were mild and infrequent. Gouze[104] found clopane to be an effective ephedrine-like compound.

Baker[13] states that the effect of sublingual administration of isopropylarterenol may be enhanced by the addition of 100 mg of benzyl nicotinamide, an antispasmodic drug. Better results are obtained, and the reduction of side effects permits larger dosage.

The effectiveness of aerosol therapy with isonorin was studied by Goldman,[102] with norisodrine by Kaufman and Farmer.[141] and with neosuprel by Herschfus et al.[115] On the whole, symptomatic relief of paroxysms occurred in a high proportion of cases.

Lewin, Mery and Huidobro[154] attempted the unique therapy of subcutaneous implantation of pellets of isopropylarterenol. The sulfate or hydrochloride salt was esterified, mixed with equal parts of cholesterol, sterilized, and implanted subcutaneously in the gluteal region by trochar. Dosage varied from 78 to 667 mg of the isuprel base; greater experience favored the higher dosage levels. Eighteen implantations in fifteen cases

of severe asthma gave good or excellent results in eight instances, satisfactory in seven, and poor in three. The duration of favorable effect averaged about forty days. Local tissue tolerance was excellent and no toxic effects noted. The results were considered sufficiently favorable to justify further study in a larger number of cases. One must question the long-range and ultimate cardiovascular and other possible deleterious effects of such prolonged and unremitting sympathetic (adrenergic) stress.

Parasympathetic Blocking Agents.—On hypothetical grounds, cholinergic blockade might be expected to be as effective as sympathomimetic drugs by providing a "medical vagotomy" and so obstructing the bronchoconstrictor influence of the vagus. A new anticholinergic drug, Prantal methylsulfate, was tried by Vickers[270] and Seidmon and Schaffer.[237] The former found that a single intramuscular injection of 10 or 15 mg relieved acute attacks in two to five minutes, often dramatically. In three cases of severe status asthmaticus no effect was noted. Seidman and Schaffer[237] employed the same drug orally in doses of 50 mg four times daily in seventy-six patients for three to six months or longer. Results were excellent in 46 per cent and good in 29 per cent of cases. Most of the failures were accounted for by special problems. There was no lessening of effectiveness over prolonged periods of treatment. Side effects were few, mild, and not cumulative. The simultaneous administration of chlortrimeton did not improve the results. It would seem logical to combine Prantal with a sympathomimetic drug.

Other Preparations.—Ogden and his co-workers[187] tried a new organic iodide, called Triode, consisting of a simple compound of refined pea starch and iodine, chemically a tri-iodide of beta amylose. It was found to be well tolerated in doses up to 140 mg of combined iodine per day, without iodism or allergic manifestations, and with only a few side reactions of minor nature.

Kauffman[140] found vitamin B_{12} ineffective in asthma in any dosage whether given by injection or orally. Caruselli[46] obtained good results in ten of twelve patients with daily oral doses of 30 mg for fifteen to twenty days.

Preliminary investigations by Engeset[80] in Norway suggested that quinacrine ("mepacrine") hydrochloride may have a specific effect on asthma.

Henriksen[114] warned of the dangers of injections of morphine or related substances. Two fatalities resulted from an acute aggravation of chronic cor pulmonale after morphine; in a case of pollen asthma, the electrocardiogram in the critical period revealed signs of acute cor pulmonale. Even codeine may be responsible for stagnation of secretions and bronchopneumonia.

TREATMENT: OTHER ASPECTS

Limber et al[156] found that enzymatic lysis of thick, tenacious respiratory secretions could be achieved by the inhalation of aerosol of crystalline trypsin. Two of their cases with bronchiectasis also had bronchial asthma and both showed marked general improvement. In one, the aerosol seemed to increase the dyspnea, although this could be controlled by oxygen and diphenhydramine hydrochloride. Others, including the reviewer, have employed aerosol of streptokinase and streptodornase for similar purposes.

Bentolila[22] found the best general anesthesia in status asthmaticus to be cyclopropane, although administration required a trained anesthetist. Other therapy should be employed first. It should not be used in patients in cardiac decompensation. Bronchial aspiration may be advantageously accomplished simultaneously.

According to Peters et al[197] smoking is completely contraindicated in asthma. Negative skin tests for tobacco products is no sign that smoking can be tolerated. If the patient continues, the best possible regimen for chronic asthma may fail. Likewise, any temporary benefit derived from smoking so-called asthma cigarettes or burning powders containing stramonium or nitrates, is nullified by the deleterious effect of the smoke itself, which aggravates the patients' bronchitis.

Recent pleas for the employment of respiratory exercises in asthma and emphysema have come from Baker,[14] Kiernander,[146] and Allan.[4] The details of technique will be found in their articles. The present reviewer feels strongly that breathing exercises are of great value in patients with poor or paradoxic diaphragmatic motion. The only explanation to account for the virtual neglect of this worthwhile therapy is the time required to instruct and supervise the patient.

After observing favorable results in twelve cases of asthma, Mendes[173] recommended administration of anterior pituitary gonadotropin. Arnoldsson and Pipkorn[9] performed pituitary implantation in fifteen cases; five were free of asthma for two weeks to three months, and one was still well after six months. Fresh calf pituitaries were used.

In a series of seventy-four asthmatic children, Nove[185] found some form of faulty jaw formation in all. Orthopedic correction was obtained by orthodontic appliances. Complete relief ensued in thirty-four cases, good results in twenty, and no benefit to the asthma in twenty. It is not clear to the reader how faulty jaw formation can have such remote effects.

ASTHMA IN CHILDREN

A recent review of pediatric asthma was contributed by Fontana.[86] The diagnostic problems have been discussed by Cotton,[59] Kempton,[144,145] and Breidahl.[34] The last-named holds that most asthma in children follows a definite syndrome of cyclic attacks in a fairly fixed order: a period of irritability lasting two hours to two days; a period of coryzal symptoms, difficult to distinguish from an infectious cold; pyrexia, with a fever usually about 100° or 101° F., occasionally up to 103° F., accompanying or following the last stage, and not the result of infection; the early cough; anorexia; abdominal pain and vomiting; and finally the "wheeze" and late cough, ultimately followed by the interval between the attacks. The correct diagnosis is often missed because of overemphasis on the coryzal symptoms and the fever. It should be stated that there are variations in the pattern, including termination at the febrile coryza stage without real asthma.

Kempton[144,145] points out that since asthma is a composite syndrome, with cause and effect, and disorder of function and structure intermingled, we should attempt not so much to diagnose the causes, as to assess the relative importance of a number of aspects, as a guide to therapy. We should appraise the severity and frequency of attacks ("A child is much more 'ikely to grow into it than out of it"); hereditary and familial tendencies, the specific hypersensitiveness, which is usually uncommon except in association with hay fever, and the rôles of respiratory infections, psychoneurosis, and emphysema and chest deformity.

The results of therapy of asthma in children has been reported in twenty- and thirty-year follow-up, respectively, by Rackemann and Edwards,[206] and Unger, Unger and Wolf.[259] The former investigators found that 30.7 per cent of their 688 childhood asthmatics "outgrew" their symptoms at the averge age of 14.7 years (range, five to thirty years), this to a large extent seeming to depend on the elimination of the cause. Many are still skin sensitive. Another 20 per cent are doing well, but must continue to avoid their allergens. An equal group have developed some other allergic manifestations. About 26 per cent still have asthmatic difficulties, which are severe in 10.9 per cent. Only 2 per cent of all cases have required hospitalization for attacks. While eleven patients died, only four (0.8 per cent of the total series) died of asthma.

A break-down according to etiologic factors reveals that patients sensitive to animals have done well, probably by reason of removal of the exciting factor. Nearly half of the food sensitive cases have lost their clinical sensitivity. Surprisingly, the group with negative skin tests seemed to have the best prognosis. Changes in the organ sensitiveness were common. Asthma sometimes recurred after free periods of ten or fifteen years. A review of older patients showed that changes in the prognosis of the disease may occur at any age.

In 306 children whose asthma began before the age of thirteen years, Unger[259] found that therapy gave complete relief in 32 per cent, marked relief in 45.5 per cent, moderate improvement in 14.7 per cent, failure in 4.9 per cent, and death in 2.6 per cent. Paroxysmal asthma had a better prognosis than did chronic asthma. The latter, however, was more amenable to therapy in children than in adults. The results in pollen asthma were the best of all groups. Of the eight deaths, three were due to asthma, and two partly so, with complicating pneumonia and acute laryngotracheobronchitis. The duration of paroxysmal asthma did not seem to alter the prognosis in children, but early onset of chronic asthma was unfavorable in both children and adults.

Fuller[92] followed 179 asthmatic children for more than six months. As a result of varied therapy, ninety had no attacks (half of them for more than one year), seventy-seven had fewer attacks, two were no better, and ten failed to report for observation.

COMPLICATIONS

A comprehensive discussion of the complications of asthma was presented by Derbes et al.[68]

The pathogenesis, clinical forms, and management of pulmonary emphysema were described by Robson[210] and Jacobs.[124] Instances of pneumothorax and interstitial or subcutaneous emphysema were reported by Mitchell and Bacal,[176] Van Wezel,[269] and Green.[105] While relatively infrequent, spontaneous pneumothorax may mask the symptoms of asthma and be a cause of death.

Cases of chronic cor pulmonale complicating asthma were studied by Gelfand[98] and Sachs et al.[219] The P-"pulmonale" pattern in the electrocardiogram is perhaps the best diagnostic index, although the electrocardiogram may be normal. The prognosis is poor, despite therapy. Lenègre's[153] investigations included right heart catheterizations on fifty asthmatics and angiocardiography and angiopneumography on fifteen. Asthma, if long continued and complicated by chronic bronchitis, pulmonary emphysema and anoxemia, may affect the right side of the heart, resulting

in cor pulmonale. This is relatively infrequent, occurring in less than 20 per cent of his cases. Angiopneumography showed a progressive diminution in the number and caliber of the distal branches of the pulmonary arteries. The pulmonary arterial pressure was found to be temporarily elevated during the asthma paroxysms but normal or subnormal between them; it became persistently elevated in the final stages of right ventricular hypertrophy and especially in right ventricular failure. It appears that the increased resistance in the lesser circulation, probably resulting from the anoxia, produces the pulmonary arterial hypertension, which in turn causes the right ventricular hypertrophy and eventually failure.

Nordlander[184] considered the relationship of asthma and goiter. While tracheal or bronchial compression from goiter may mimic asthma, it really produces an inspiratory stridor. In patients with both conditions, combined symptoms result. In a number of cases with both, potassium iodide therapy for months or years had no adverse effects except for one instance of thyrotoxicosis which was probably coincidental. Both hyperthyroidism and myxedema impairs the general condition of the asthmatic. In one patient, thyroid therapy of myxedema provoked an asthma which was very resistant to therapy.

Frohlich[89] reported a case of primary amenorrhea associated with severe bronchial asthma. A number of courses of synapoidin therapy resulted in the establishment of irregular menstruation, in the development of secondary sex characteristics, and simultaneously in a marked improvement in the asthma.

In a patient observed by Whitney,[283] heparin and dicumarol therapy of a phlebothrombosis was followed by extensive abdominal wall and intra-abdominal hemorrhage of severe degree, as found at surgery. The hemorrhage was thought to be initiated by the rupture of blood vessels resulting from the coughing spasms of status asthmaticus.

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SECOND INTERNATIONAL CONGRESS OF CARDIOLOGY

The Second International Congress of Cardiology will be held in Washington, D. C., September 12 to 15, 1954. It will be immediately followed by the Annual Scientific Sessions of the American Heart Association, September 16 to 18, 1954. The opening session will be held in the auditorium of Constitution Hall at 10:30 a.m. on Sunday, September 12, 1954, with addresses of welcome. A reception will be given at the Mayflower Hotel at 5:00 p.m. on the same day for all members of the Congress and their families. A banquet will be held September 15, 1954, at 7:30 p.m.

The Scientific Sessions lasting for three days will include formal papers, panel discussions, clinical pathological conferences and visits to important medical centers in Washington and Bethesda. The program will be printed in French, Spanish and English. Immediate translation of some of the papers and discussions will be made in three languages.

A series of Post-Congressional visits and conferences to at least twenty of the leading cardiac clinics in different parts of the United States and Canada has been arranged by special committees of local Heart Associations in the various cities.

L. W. GORHAM, *Secretary-General*

In Memoriam

NOAH FOX

Noah Fox was born in Greenview, Illinois, March 22, 1896. He was a graduate of Crane High School, received his B.S. degree from the University of Chicago and his M.D. degree from the Rush Medical School. He served his internship at the Cook County Hospital, and took postgraduate studies at the University of Chicago in research, pharmacology and anatomy. Doctor Fox held teaching positions at the University of Chicago from 1924 to 1929, and at the time of his death, on April 9, 1953, he was Assistant Professor of the Department of Otolaryngology, University of Illinois, Chairman of the Departments of Otolaryngology of the Mother Cabrini Hospital and the Jackson Park Hospital, and was also Staff Member of the Illinois Central Hospital. He was a member of Sigma Xi, and many medical societies, including the American Academy of Ophthalmology and Otolaryngology, a Fellow of the American College of Surgeons, and member of the Chicago Otolaryngologic Society, Chicago Medical Society and a Diplomate of the American Board of Otolaryngology. He was an active member of the American College of Allergists.

Doctor Fox had a great interest in horticulture, to which he devoted considerable time. He had a greenhouse built on the grounds of his home where he raised camelias, and many other flowers and plants. At his country home in Momence, Illinois, Doctor Fox grew many varieties of trees, including fruit trees, shade and ornamental trees, evergreens, and shrubs.

Doctor Fox is survived by his wife, Beatrice Sender Fox, his son, Eugene N. Fox, aged twenty-five, who is completing work on his doctorate in Microbiology at Western Reserve University, and his daughter Caryl, aged twenty-two, who graduates in June from the University of Wisconsin. Four brothers and three sisters also survive him; brothers, Rabbi G. George, J. Logan, Hershey and Matthew; sisters, Clara, Elizabeth and Ethel.

Members of the College extend their sincere sympathy to the family and friends.

But life is sweet, though all that makes it sweet
Lessens like sound of friend's departing feet;
And death is beautiful as feet of friend
Coming with welcome at our journey's end.

GEORGE WILLIAM CURTIS

News Items

THE CALIFORNIA SOCIETY OF ALLERGY

At its annual meeting, The California Society of Allergy elected the following officers for 1953-1954:

President—Grace M. Talbott, M.D., San Francisco.

President-Elect—Norman Shure, M.D., Los Angeles.

Secretary-Treasurer—Lazarre J. Courtright, M.D., San Francisco.

POSTGRADUATE COURSE IN PEDIATRIC ALLERGY

Under the direction of Dr. Bret Ratner, Professor of Clinical Pediatrics and Associate Professor of Immunology, and member of those departments, at New York Medical College, Flower and Fifth Avenue Hospitals, a postgraduate course in Pediatric Allergy will be held November 4, 1953, through May 31, 1954, consisting of thirty sessions, Wednesdays 9 a.m. to 4 p.m. The fee is $300.00.

This course consists of lecture-seminars, laboratory and clinical procedures, clinic work, ward rounds, and animal experimentations. Lecture-seminars cover the basic principles, diagnosis and treatment of allergy in children and applied immunology.

Applicants must be certified in pediatrics or have the requirements for certification. The group is limited. Applications should be made to: Dean, New York Medical College, 106th Street and Fifth Avenue, New York 29, N. Y.

A one-year Research Fellowship in Pediatric Allergy is also available starting January, 1954. Application should be made now.

CANADIAN ACADEMY OF ALLERGY MEETING

June 16, 1953

Royal Alexandra Hotel, Winnipeg, Manitoba

Morning Session—9:30 A.M.

Studies on Urinary Histamine—Drs. J. Mitchell, Charles F. Code and George P. Logan, Mayo Clinic, Rochester, Minnesota.

Histamine Symposium

1. Roles of Histamine in the Anaphylactic Reaction in Guinea Pigs and Rabbits—Dr. C. F. Code, Mayo Clinic Foundation, Rochester, Minnesota.
2. Liberation of Histamine and Other Substances during Anaphylactic Reactions in Dogs and Monkeys—Dr. L. B. Jacques, Professor of Physiology, University of Saskatchewan, Saskatoon.
3. Role of Histamine in Allergic and Anaphylactic Reactions in Man—Dr. Bram Rose, McGill University, Montreal.

Afternoon Session—2:00 P.M.

Recent Advances in ACTH and Cortisone in Allergy—Dr. Bram Rose, Montreal.

Concepts on Mode of Action of Salicylates—Dr. L. B. Jacques and Dr. J. Lowenthal, University of Saskatchewan, Saskatoon.

Experience with Pollen Surveys in Manitoba from 1939 to 1952—Dr. C. H. A. Walton and Dr. M. G. Dudley, Winnipeg.

Recent Advances in Bacterial Allergy—Dr. K. A. Baird, St. John, N. B.

Clinical and Experimental Allergic Cephalalgia—Dr. Jacques Leger, Montreal.

Effect of Antihistamines on Smooth Muscle—Dr. T. H. Aaron and Dr. W. Stewart, Edmonton.

REACTION TO PENICILLIN PREPARATIONS

The following communication was sent under date of May 20, 1953.

Recently several reports have been published concerning acute anaphylactic reactions following administration of various penicillin preparations. Some of these have terminated fatally within a few minutes in spite of resuscitative measures. Although still quite rare, there appears to have been an increase in the number of these reactions during the past year. In practically all of the cases that have come to our attention the drug was administered intramuscularly, although there have been reports of one or two cases following oral administration of tablets or troches. Similarly, a few cases have resulted from inhalation of penicillin aerosols or instillation into the sinus cavities.

In view of the above, it is our feeling that the circulars and brochures for penicillin preparations should include a statement informing the physician of the possibility of anaphylactic reactions following the use of penicillin to the effect that:

"The injection of penicillin in rare instances may cause acute anaphylaxis. The reaction appears to occur more frequently in patients with bronchial asthma, other allergies, or those who have previously demonstrated a sensitivity to penicillin. Care should be taken to avoid accidental intravenous administration, and resuscitative drugs, such as epinephrine, antihistamines, aminophylline, et cetera, should be readily available for emergency intravenous administration."

A statement embodying the above should be included in the next printing of your circulars and brochures covering parenteral, oral, and aerosol penicillin, and for penicillin recommended for instillation into body cavities.

HENRY WELCH, *Director*
Division of Antibiotics
Department of Health, Education, and Welfare
Food and Drug Administration

PUBLICATION OF RESOLUTIONS

By action of the Board it was decided that there shall henceforth be full publication in the ANNALS of all resoutions formally and finally adopted and approved by the Board of Regents at either the general or special meetings of the Board.

BOOK REVIEWS

1953 MEDICAL PROGRESS. A Review of Medical Advances During 1952. Edited by Morris Fishbein, M.D., Clinical Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill. 301 pages. New York and Toronto: The Blakiston Company, 1953. Price $5.00.

This first volume, in a series, contains 17 chapters each of which is written by a specialist in the field, and includes new developments in: Cardiology-heart disease; surgery; infectious diseases; arterial hypertension; rheumatic diseases; nutrition; new and important drugs and medications; dermatology; urology; psychiatry and psychosomatic medicine; obstetrics; diseases of the chest; ear, nose and throat; gastrointestinal disorders; allergy; orthopedic surgery. The chapter on allergy by Dr. Leon Unger and Dr. Albert H. Unger is well organized and is an up-to-date, succinct condensation of our present knowledge of the diagnosis and management of allergic diseases. This subject is especially significant now for general practitioners, because everywhere it is recognized that conditions affecting the skin may have fundamental reflections in the whole character of the human body. There is an excellent over-all review of the whole change in point of view regarding psychiatry and psychosomatic medicine and the large part it plays in handling every form of human disease. The final summary on medical advances by the editor emphasizes what he considers the most important and significant advances in medicine during 1952.

This book is written primarily for the busy general practitioner. It is attractively bound and printed.

THE 1952 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. Edited by Marion B. Sulzberger, M.D., Professor and Chairman, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School; and Rudolf L. Baer, M.D., F.A.C.A., Associate Professor of Clinical Dermatology and Syphilology, New York University Post-Graduate Medical School. 444 pages, 67 illustrations. Chicago: Year Book Publishers, 1953. Price $6.00.

The 1952 Year Book contains a new subsection on Endocrine Therapy, in addition to its valuable abstracts of important findings in the field of Dermatology and Syphilology. The new subsection appeared desirable in view of the expanding usefulness of ACTH and cortisone. The year's work includes numerous reports indicating the increasing value of these hormones in judiciously selected, severe cases of common benign dermatoses, such as atopic dermatitis, contact dermatitis and drug eruptions, provided proper precautions are observed. Moreover, in contrast to cortisone, hydrocortisone (compound F) has been shown to have considerable promise as a local external therapeutic agent in selected common dermatoses as well as being effective on intracutaneous injection in some skin lesions and skin reactions. Many items of progress for the year include new knowledge of melanogenesis and treatment of hyper- and depigmentations, new evidence that not all melanomas are as highly malignant as formerly supposed and that radical mutilating surgery does not materially improve the prognosis and survival period in patients with melanoma; progress in treatment of severe systemic fungous infections through use of stilbene derivatives; new information on safety limits of superficial dermatologic roentgen therapy; additional knowledge of common stigmas found in patients with atopic dermatitis, particularly the abnormal sweat responses, vascular responses and reactions to heat, cold and injections of acetylcholine; and more fundamental information on the L. E. phenomenon, on the chemical composition of the nuclear material and on the interrelated roles of the toxic serum fraction and phagocytic cells.

The book is divided into ten topics covering treatment and prevention, eczematous dermatitis, atopic dermatitis and urticaria, allergy, drug eruptions, miscellaneous dermatoses, cancers and tumors, venereal diseases, investigative studies and miscellaneous topics.

The critical editorial comments following many of the abstracts are one of the most valuable features of the book. The book is well indexed. It is difficult to publish good illustrations of skin lesions and the publishers are to be complimented on their excellent clarity.

STEROID METABOLISM AND ESTIMATION. Vol. II (of a series of 4 volumes). Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. Proceedings of the Symposium held in London under the auspices of the Ciba Foundation. 429 pages, 96 illustrations. Philadelphia and New York: The Blakiston Company, 1952. Price $6.75.

This is the second volume in a series of four, containing reports from the Symposium on Endocrinology held in London. Book I of this volume covers chemistry and estimation of urinary metabolites of progesterone and of urinary estrogens, urinary corticoids and 17-ketosteroids, steroid isolation, estimation of progesterone metabolites in blood, placental extracts and bile. Book II covers metabolism of C_{19} steroids, excretion of steroid alcohols and estrogens, metabolism of neutral C_{21} steroids, progesterone metabolism, blood progesterone in pregnancy, metabolism of progesterone and its biological activity. General discussions follow each chapter.

The volume is compact, well bound and printed.

ENDOCRINE TREATMENT IN GENERAL PRACTICE. Edited by Max A. Goldzieher, M.D., Endocrinologist, St. Clare's Hospital, New York, and Joseph W. Goldzieher, M.D., Research Associate, New York Medical College, New York. 488 pages, 19 illustrations. New York: Springer Publishing Company, Inc., 1953. Price $8.00.

This book covers hormone therapy for all diseases in which the authors have found such treatment to be effective, practical and safe, and is written for the general practitioner. The arrangement is from a symptomatic point of view, the authors state the diagnostic considerations and discuss the endocrine treatment they recommend. There are thirty chapters written by twenty-one contributors, each for his special field, including the final chapter of currently available hormone preparations and dosages.

The comment on extrinsic allergic asthma, although brief, is pertinent. Hormonal treatment of allergic asthma is reserved for acute emergencies of status asthmaticus. The initial control of symptoms by intravenous therapy consists of a course of ten days to two weeks, using either ACTH by injection or oral cortisone. Occasionally, in the young individual, where infection is a factor, continuous therapy may be necessary. When other methods appear to have failed, obviously it is justifiable to use continuous therapy in the form of oral cortisone in doses ranging from 50 to 100 mg per day according to need, with the usual precautions taken. It is refreshing, in the light of our knowledge of these hormones, to find that the authors state that in the treatment of asthma the use of ACTH or cortisone should be avoided in children with the exception of the handling of acute crises. The group of adults presenting symptoms of dyspnea associated with wheezing and cough but no sputum, with weakly positive skin reactions to inhalants with no clinical significance, and with a nearly chronic bronchial spasm, with or without moderate emphysema, who are frequently sensitive to aspirin, offers great difficulties. In these cases ACTH or cortisone soon loses its effect even though there is a drop in eosinophils.

There is a diet booklet and chart included and these may be ordered from the publishers. The book is very completely indexed, neatly bound and printed.

THE HEBREW MEDICAL JOURNAL—HAROFÉ HAIVRI. Vol. 2, 1952. Edited by Moses Einhorn, M.D. Published semi-annually. 983 Park Avenue, New York 28, N. Y.

Twenty-five years ago a group of physicians came together in New York seeking the revival of medical science in the Hebrew language, and established a medical journal of modern periodic literature, published semi-annually with English and Hebrew versions of medical articles in each volume. HAROFÉ HAIVRI celebrates its Twenty-fifth Anniversary Year with Volume 2 of 1952. The dedicated group of American Jewish physicians who began the Journal had several goals, but the principal one was to enlarge the medical terminology in the Hebrew language. The Editors reveal that these American Jewish scholars have rescued from oblivion fourteen hundred years of development of a scientific medical terminology created by Jews in their own Hebrew tongue. The American physicians contributing to HAROFÉ HAIVRI, according to the Editors, devote themselves more to the field of medical language than to the field of medicine as a science itself. However, significant contributions to medical literature have been made through the pages of this Journal, and in the various departments will be found ancient manuscripts, medical history, medicine in the Bible, medicine in the Talmud, and Palestinian medicine.

We extend sincere congratulations to the editors and publishers of HAROFÉ HAIVRI, and express the hope that their important work may continue in the years ahead.

IMMUNITY HYPERSENSITIVITY-SEROLOGY. Sidney Raffel, Sc.D., M.D., Professor of Bacteriology and Experimental Pathology, Stanford University School of Medicine, California. 531 pages. New York: Appleton-Century-Crofts, Inc., 1953. Price $8.00.

The author successfully bridges the broader concept of the word *immunity*. Antibody-reacting systems in general are often considered as immunologic, whereas in many cases there is no relationship to immunity. The science of immunity embraces native and acquired resistance to disease-producing agents in which biologic, chemical and physical factors play a role. Humoral antibodies do not necessarily become the major factors of immunity, although they undoubtedly are in a few diseases. Antibodies appear regularly during the course of disease as a physiologic response of the tissues to foreign substances regardless of their usefulness to the body. Their extremely high degree of specificity to reacting substances makes them instruments for the recognition of proteins and polysaccharides, or for the classification of cells such as human red cells and bacteria. It is evident that these processes have no direct connection with immunity; their mechanism may also play a part in immunity. Serology describes studies of antibody reaction. Immunologists can no longer confine their perspective of the whole field of immunity to the activities of antibodies. Throughout the book the author's intention is to describe the phenomena of immunity in basic terms, particularly concerning the resistance to bacteria, viruses and toxins. The author deals at length on the consideration of serology since our major information is derived from serologic reactions, but they are considered secondary to the general problem of immunity and as being separate from immunity in respect to considerations of blood group reactions.

There are four sections. The first twelve chapters deal with the various mechanisms of native and acquired immunity and factors influencing immunity. Section two has four chapters on hypersensitivity, immediate, delayed, and relation of hypersensitivity to immunity, as well as other hypersensitive and hypersensitive-like states. Section three contains thirteen chapters dealing with the mechanism of resistance in various infectious diseases, and section four contains three chapters on serology and antigenic systems, including microbial antigens and toxins and cellular and blood cell

antigens. There is a comprehensive, authoritative bibliography following each chapter, with numerous figures. The format is excellent and every allergist interested in a broad concept of immunologic mechanisms should have this book at hand for ready reference.

CONTACT DERMATITIS. George L. Waldbott, M.D., Senior Physician, Harper Hospital, Chief of Division of Allergy, Assistant Physician, Grace Hospital, Chief of Allergy Clinic, Children's Hospital, Detroit, Michigan. 218 pages, 131 illustrations. Springfield: Charles C Thomas, 1953. Price $8.75.

This is one of the most succinct and practical monographs on the subject of contact dermatitis extant. It is also well illustrated. The author's broad experience for many years with hospital and private clinic patients qualifies him as an authority on the subject. He has been particularly interested and has written extensively on the subject in medical journals. This is a compact crystallization of this information. There is no more difficult problem that is met by the general practitioner, the dermatologist or allergist than determining the cause of contact dermatitis. Proctologists and gynecologists will also appreciate the unique method of analyzing and treating pruritus ani and pruritus vulvae. The text is so written that those who have chronic cases of contact dermatitis may acquire valuable information concerning the disease so that the doctor may wish to have the patient read the pertinent parts of this monograph. It is necessary, therefore, to include an extensive glossary of elementary terms. What general practitioner or specialist would not be interested in subjects such as, "What produces dermatitis year after year about July Fourth," or the source of a "honeymoon dermatitis," and how we can distinguish between a ringworm infection and dermatitis from footwear, how can we manage a dermatitis refractory to treatment, and why does a case of ivy poisoning require six weeks to heal, whereas other forms of contact dermatitis clear up within seven to ten days. The black and white photographs of the lesions are very illustrative and definitive. There are ten chapters, including an appendix listing the principal contact agents and other contributing irritants to be considered in various occupations, as well as a preparation of poison ivy extract and a pollen oil and control of poison ivy plants. There is a comprehensive and pertinent bibliography and the book is well indexed. The various chapters deal with the mechanism, pathology, diagnosis, etiology and patterns of the various domains of the body, special situations, and therapy, including prophylactic treatment, densensitization technique, symptomatic treatment and general measures, including specific prescriptions. The reviewer has already found the book invaluable as a reference.

CHRONIC PULMONARY EMPHYSEMA, Physiopathology and Treatment. By Maurice S. Segal, M.D., Clinical Professor of Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital, and M. J. Dulfano, Resident, Department of Inhalational Therapy, Boston City Hospital; Research Fellow in Medicine, Tufts College Medical School, Boston, Mass. 180 pages, 31 figures. New York: Grune & Stratton, 1953. Price $5.50.

Not many years ago, emphysema was considered in the group of chronic diseases for which no treatment was available. Not very much was known about it and the few therapeutic measures that were used seemed to give, at the best, mild and temporary palliation. In recent years, more attention has been directed to this disease; and a great deal of work has been done on etiological factors, and in the development of the successful methods of treatment. It is true that much remains to be done. But, the understanding of the pathology and the development of therapy has progressed to a point that all physicians, who are involved in bronchial disturbances of any sort, must be aware of this developing therapy. Under these circumstances, it is timely to have a monograph on chronic pulmonary emphysema.

This volume is particularly directed to those who have some special knowledge on both bronchial and pulmonary diseases. But, it is so written that those whose major interest is simply in learning how to handle a particular case of emphysema can also use it as a reference volume.

From the standpoint of the allergist, the chapter on the development of emphysema is a particularly important one, since the understanding of the problem may enable an attending physician to actually prevent this unpleasant complication. In fact, a great many of the physiologic concepts upon which therapy has been developed depend upon the information set forth in this chapter.

In regard to therapy itself, the authors have emphasized, and I believe correctly so, that there are many facets in the course of treatment which may vary with the individual and with the case. They range from various drugs to inhalation therapy, with and without mechanical aids, and includes such procedures as pneumoperitoneum and breathing exercises. It is a large subject, and a difficult one to cover in a monograph. The result is a meaty book whose pages are filled with concentrated information.

Those who see only an occasional case of emphysema should read it carefully, because it gives a broad base upon which treatment can be developed. Those whose practice includes many emphysematous patients would do well to use this little monograph as a reference volume, since these patients notoriously show the most distressing individual variations and frequently do not continue to improve as much as is anticipated. For those who deal in industrial matters who must consider degrees of disability, the chapter on pulmonary function tests and the appendix on methodology will be of additional value.

This is a well-organized and concise volume, and should become a popular handbook.

E.R.L.